BRCA Carriers –

Clinical Recommendations for

Gastric cancer

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הכנס הישראלי הרב-תחומי לסרטן תורשתי
1/2026

Sub-committee members:

- Dr. Shira Shur (Shamir MC)
- Dr. Sari Liberman (Genetics, Shaare Zedek MC)
- Prof. Lior Katz (Hadassa MC)

Topics for decision

1. Gastroscopy for all BRCA carriers ? Protocol ?
2. Place of FH
3. Test and treat for HP ? When ?

Gastroscopy for all BRCA carriers

Factors to be considered:

- GC rate in Israel
- Mortality rate
- Efficiency of gastroscopy for screening
- Complications (negligible)
- Carrier rate of BRCA
- RR of GC in carriers

GC in Israel

- In 2020, the age-specific rates of stomach cancer, by gender and population group, were as follows:

	Arabs				Jews/others			
	Males		Females		Males		female	
	cases	Rate/100,000 population	cases	Rate/100,000 population	cases	Rate/100,000 population	cases	Rate/100,000 population
under 5	.	.	.	.	.	.	.	.
5 to 9	.	.	.	.	.	.	.	.
10 to 14	.	.	.	.	.	.	.	.
15 to 19	.	.	.	.	.	.	.	.
20 to 24	.	.	.	.	.	.	1	0.43
25 to 29	.	.	.	.	1	0.43	.	.
30 to 34	2	3.05	2	3.11	1	0.42	3	1.27
35 to 39	1	1.77	1	1.8	2	0.85	1	0.42
40 to 44	1	1.77	5	8.94	10	4.48	5	2.18
45 to 49	2	3.84	1	1.95	10	4.82	9	4.2
50 to 54	6	13.67	.	.	11	6.34	12	6.63
55 to 59	6	16.53	1	2.69	23	14.6	17	10.08
60 to 64	6	23.26	3	11.07	36	23.3	18	10.47
65 to 69	10	55.56	4	20	51	33.93	22	12.88
70 to 74	7	61.4	5	38.17	75	58.09	39	25.66
75+	9	58.82	8	40.2	124	72.56	94	39.2

Based on the age-specific rates, the cumulative rate of stomach cancer would be 1198.4/100,000 in **Arab men**, 639.6/100,000 in **Arab women**, 1099.2/100,000 in **Jewish/Other men** and 567.0/100,000 in **Jewish/other women** or **1.2%, 0.6%, 1.1% and 0.6%,** respectively. (Barbara Silverman, Director, Israel National Cancer Registry at Israeli ministry of health)

Mortality rate of GC

- USA –< 25% diagnosed at early stage
- 5 years survival 32%

- Far East – 60-70% are diagnosed at early stage
- 5 years survival ~ 70%

Efficiency of Gastroscopy

Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review

Xing Zhang,[1,2,*] Meng Li,[1,2,*] Shuntai Chen,[1,2,*] Jiaqi Hu,[1,2,*] Qiujun Guo,[1,*] Rui Liu,[1] Honggang Zheng,[1] Zhichao Jin,[1] Yuan Yuan,[1,2] Yupeng Xi,[1,2] and Baojin Hua[1]

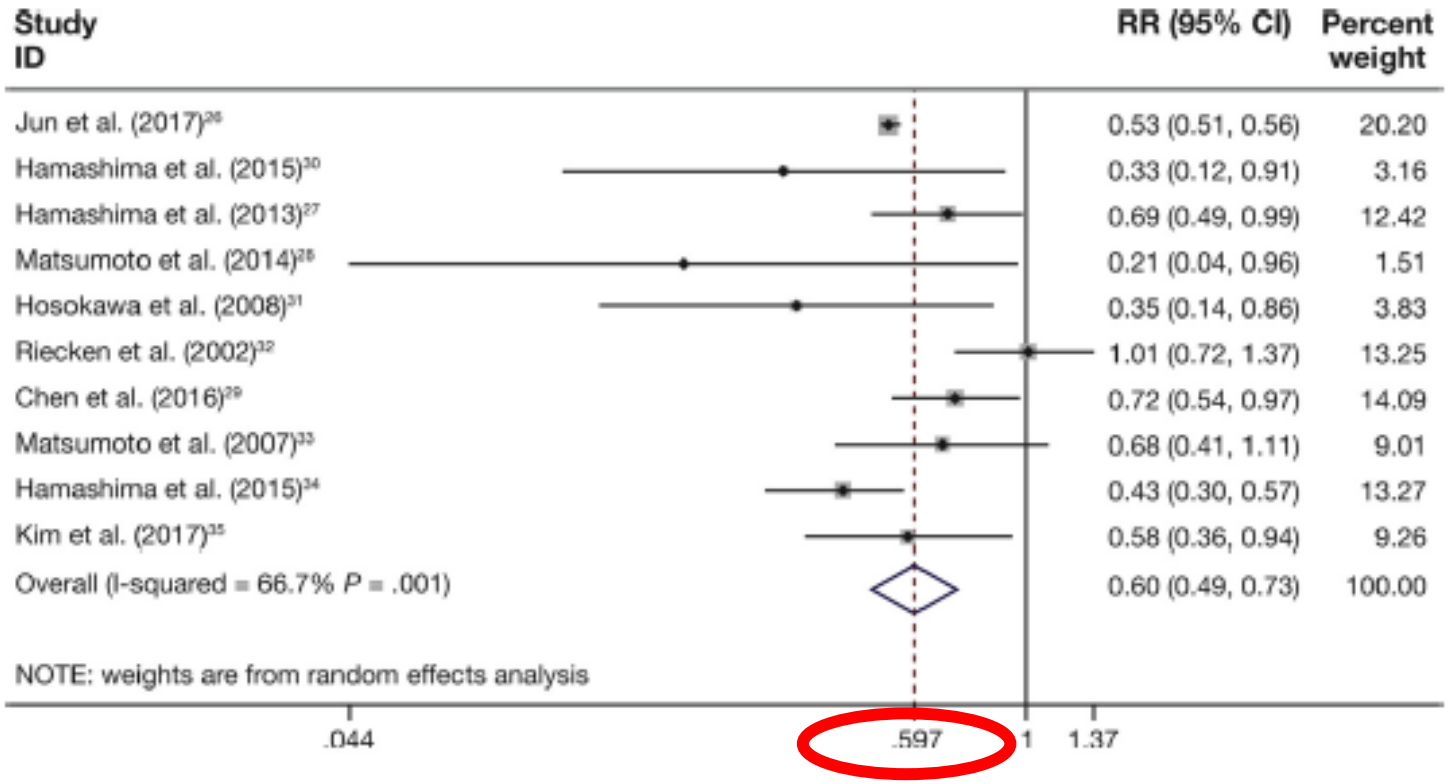

Figure 2. Forest plot of reduction of gastric cancer mortality after endoscopic screening. ID, identification.

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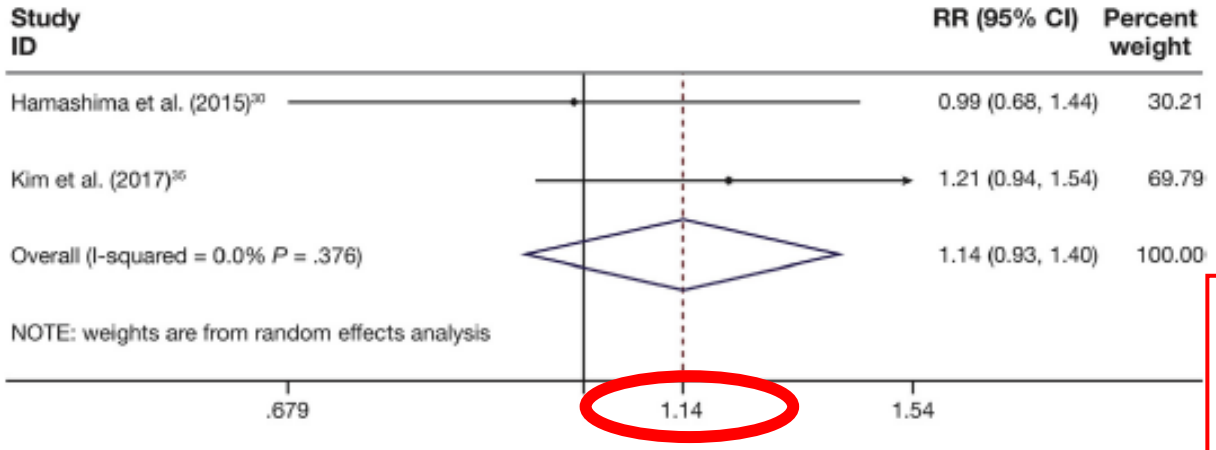

Figure 3. Forest plot of gastric cancer incidence after endoscopic screening. ID, identification.

Efficiency of Gastroscopy

Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review

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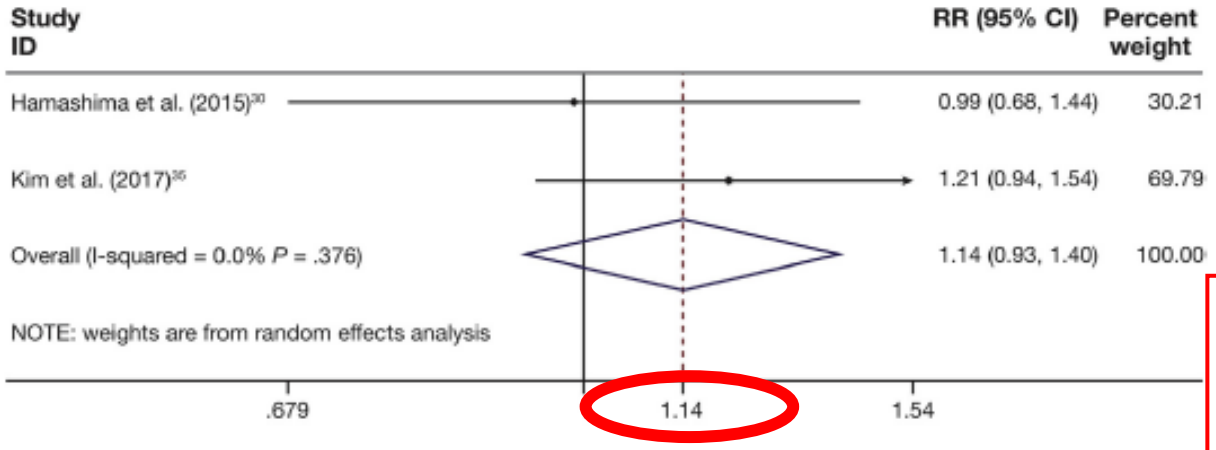

Figure 3. Forest plot of gastric cancer incidence after endoscopic screening. ID, identification.

- Miss rate of 10% for GC (Quality..)

BRCA carrier rate

- General population – 1:280, AJ – 1:40
- BRCA carriers > 50y – 15,000- 23,000

GC in BRCA carriers

- Literature review – search words: BRCA, HBOC, gastric/stomach carcinoma /cancer, Helicobacter
- 484 studies, including 21 leading original articles, reviews and meta-analyses

Table 1. Select Studies Reporting Gastric Cancer Risk in *BRCA1* Carriers

Author	Year	Population Location	Patient Population	Comparator Cohort	Risk Estimates	Gastric Cancer Risk Increased?
Gastric Cancer Risk in *BRCA1* PV Carriers						
Ford et al. [41]	1994	North America and Western Europe	464 *BRCA1* PV carriers	General Population	1 observed case vs. 0.76 cases expected; RR 1.11, $p > 0.05$	No
Johannsson et al. [27]	1999	Sweden	1145 relatives from 29 families with a proband with a *BRCA1* PV	General Population	All: SMR 2.76, 95% CI 1.01–6.00; F: SMR 5.16, 95% CI 1.14–13.22; M: SMR 1.43, 95% CI 0.17–5.15	Yes
Risch et al. [38]	2001	Canada	39 *BRCA1* PV carriers and 291 FDRs	4378 FDRs of ovarian cancer patients without *BRCA1* or *BRCA2* PVs	Incidence: 4.9% vs. 0.8%; RR 6.2, 95% CI 2.0–19	Yes
Brose et al. [39]	2002	United States	483 *BRCA1* PV carriers	General Population	Age-adjusted lifetime risk: 5.5% vs. 0.8%, 95% CI 3.4–7.5%	Yes
Thompson et al. [42]	2002	North America and Western Europe	2245 *BRCA1* PV carriers	General Population	RR 1.56, 95% CI 0.91–2.68	No
Schlebusch et al. [26]	2010	South Africa	793 individuals from 26 families with a *BRCA1* PV	General Population	7 cases observed vs. 6.62 cases expected, $p = 0.8829$	No
Moran et al. [23]	2012	England	631 *BRCA1* PV carriers and 1184 FDRs from 268 families with a *BRCA1* PV	General Population	RR 2.4, 95% CI 1.2–4.3	Yes
Mersch et al. [43]	2014	United States	613 *BRCA1* PV carriers	General Population	SIR 1.736, 95% CI 0.023–9.661	No
Li et al. [15]	2022	Multinational (>10 countries)	8884 *BRCA1* PV carriers	General Population	RR 2.17, 95% CI 1.25–3.77	Yes
Meta-analysis						
Lee et al. [45]	2021	North America, Western Europe, South Africa	Meta-analysis, including 5 studies pertaining to *BRCA1* PVs, all of which are cited in this sub-section of Table 1 [23,28,38,42,43]	Varied by study	*BRCA1* PVs were not associated with increased risk of GC (RR 1.70, 95% CI 0.93–3.09)	No

Table 2. Select Studies Reporting Gastric Cancer Risk in *BRCA2* Carriers.

Author	Year	Population Location	Patient Population	Comparator Cohort	Risk Estimates	Gastric Cancer Risk Increased?
Gastric Cancer Risk in *BRCA2* PV Carriers						
Breast Cancer Linkage Consortium [28]	1999	Europe and North America	1152 confirmed or probable *BRCA2* PV carriers from 173 families *	General Population	RR 2.59, 95% CI 1.46–4.61	Yes
Johannsson et al. [27]	1999	Sweden	728 relatives from 20 families with a proband with a *BRCA2* PV	General Population	All: SMR 1.63, 95% CI 0.34–4.75; F: SMR 1.37, 95% CI 0.03–7.64; M: 1.79, 0.22–6.48	No
Risch et al. [38]	2001	Canada	21 *BRCA2* PV carriers and 160 FDRs	4378 FDRs of ovarian cancer patients without *BRCA1* or *BRCA2* PVs	Incidence: 1.8% vs. 0.80%; RR 2.3, 95% CI 0.30–18	No
Tulinius et al. [46]	2002	Iceland	90 families with a proband with a *BRCA2* PV	General Population	F FDRs: RR 1.78, 95% CI 0.57–4.10; F SDRs: RR 3.08, 95% CI 2.09–4.34; M FDRs: RR 2.40, 95% CI 1.29–4.05; M SDRs: RR 1.91, 95% CI 1.33–2.63	Yes
van Asperen et al. [48]	2005	Netherlands	1811 individuals with a 50% probability of having a *BRCA2* PV	General Population	RR 1.2, 95% CI 0.6–2.0	No
Schlebusch et al. [26]	2010	South Africa	1264 individuals from 43 families with a *BRCA2* PV	General Population	24 cases observed vs. 11.17 cases expected, $p = 0.0001$	Yes
Moran et al. [23]	2012	England	517 *BRCA2* PV carriers and 1009 FDRs from 222 families with a *BRCA2* PV	General Population	RR 2.7, 95% CI 1.3–4.8	Yes
Mersch et al. [43]	2014	United States	459 *BRCA2* PV carriers	General Population	SIR 1.755, 95% CI 0.023–9.763	No
Li et al. [15]	2022	Multinational (>10 countries)	6095 *BRCA2* PV carriers	General Population	RR 3.69, 95% CI 2.40–5.67	Yes
Meta-analysis						
Lee et al. [45]	2021	North America, Western Europe, South Africa	Meta-analysis, including 6 studies pertaining to *BRCA2* PVs, all of which are cited in this sub-section of Table 2 [23,25,28,38,43,49]	Varied by study	*BRCA2* PVs were associated with increased risk of GC (RR 2.15, 95% CI 1.98–2.33)	Yes

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

J Clin Oncol 40:1529-1541. © 2022

- Western population

- This study investigated the associations between the risks of 22 cancers and BRCA1/2 PVs using data from > 5,300 families segregating BRCA1/2 PVs, from the Consortium of Investigators of Modifiers of BRCA1/2

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
Connective and soft tissue	30-79	0.80 (0.07 to 8.71)	.86	0.17 (0 to 25.94)	.49
Corpus uteri	40-79	0.97 (0.35 to 2.70)	.95	0 (0 to 3.2E+280)	.94
Esophagus	40-79	0.96 (0.35 to 2.65)	.93	0.85 (0.29 to 2.49)	.77
Eye	30-79	1.56 (0.23 to 10.77)	.65	4.60 (1.00 to 21.16)	.05
Gallbladder and extrahepatic ducts	40-79	3.34 (1.34 to 8.28)	.01	2.28 (0.77 to 6.70)	.14
Head and neck	40-79	1.13 (0.49 to 2.62)	.78	0.71 (0.18 to 2.86)	.63
Kidney	40-79	1.84 (0.74 to 4.56)	.19	0.26 (0.01 to 6.20)	.41
Leukemia	20-79	0.90 (0.36 to 2.26)	.82	0.91 (0.29 to 2.85)	.87
Lung	40-79	1.37 (0.85 to 2.21)	.19	1.13 (0.63 to 2.03)	.68
Lymphoma	20-79	1.03 (0.33 to 3.22)	.96	0.97 (0.16 to 5.87)	.97
Melanoma	40-79	0.64 (0.14 to 2.95)	.56	0.93 (0.26 to 3.25)	.91
Multiple myeloma	30-79	3.06 (0.83 to 11.26)	.09	0.84 (0.10 to 7.31)	.87
Pancreas	30-79	2.36 (1.51 to 3.68)	< .001	3.34 (2.21 to 5.06)	< .001
Prostate	40-79	0.82 (0.54 to 1.27)	.38	2.22 (1.63 to 3.03)	< .001
Stomach	30-79	2.17 (1.25 to 3.77)	.01	3.69 (2.40 to 5.67)	< .001
Testis	20-79	0.07 (0 to 1.63)	.10	2.17 (0.82 to 5.70)	.12
Thyroid	30-79	0.14 (0.01 to 1.55)	.11	0.84 (0.22 to 3.24)	.80

TABLE 4. Age-Specific Absolute Risks (%) and 95% CIs of Primary Cancers With Significant Associations for *BRCA1* and *BRCA2* Carriers[a]

Cancer Site	Sex	Age 50 Years	Age 60 Years	Age 70 Years	Age 80 Years
Absolute risk (95% CI) for *BRCA1* carriers					
Breast	Male	0.02 (0.01 to 0.08)	0.07 (0.02 to 0.3)	0.2 (0.05 to 0.7)	0.4 (0.1 to 1.5)
Pancreas	Male	0.1 (0.07 to 0.2)	0.4 (0.3 to 0.7)	1.3 (0.8 to 2.0)	2.9 (1.9 to 4.5)
	Female	0.08 (0.05 to 0.1)	0.3 (0.2 to 0.5)	1.0 (0.6 to 1.5)	2.3 (1.5 to 3.6)
Stomach	Male	0.2 (0.1 to 0.3)	0.6 (0.3 to 1.0)	1.1 (0.6 to 2.2)	1.6 (0.7 to 4.0)
	Female	0.1 (0.06 to 0.2)	0.3 (0.2 to 0.5)	0.5 (0.3 to 0.9)	0.7 (0.3 to 1.7)
Absolute risk (95% CI) for *BRCA2* carriers					
Breast	Male	0.2 (0.1 to 0.5)	0.7 (0.4 to 1.5)	1.8 (0.9 to 3.7)	3.8 (1.9 to 7.7)
Pancreas	Male	0.2 (0.1 to 0.3)	0.9 (0.5 to 1.4)	2.0 (1.2 to 3.3)	3.0 (1.7 to 5.4)
	Female	0.2 (0.09 to 0.2)	0.6 (0.4 to 1.0)	1.5 (0.9 to 2.5)	2.3 (1.3 to 4.2)
Prostate	Male	0.2 (0.2 to 0.3)	2.9 (2.1 to 3.9)	12.6 (9.4 to 16.7)	25.9 (20.5 to 31.7)
Stomach	Male	0.1 (0.08 to 0.2)	0.5 (0.3 to 0.8)	1.4 (0.8 to 2.3)	3.5 (2.1 to 6.1)
	Female	0.2 (0.1 to 0.4)	0.6 (0.3 to 1.0)	1.3 (0.7 to 2.5)	3.5 (1.9 to 6.4)

[a]Absolute risks were calculated on the basis of UK cancer incidences in years 2008-2012 in the Cancer Incidence in Five Continents.[26]

Gastroscopy for all BRCA carriers ?

- Not really, d/t low GC rate in general population and RR of 1.5-2.5 in carriers

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BUT …

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AGA Clinical Practice Update on Screening and Surveillance in Individuals at Increased Risk for Gastric Cancer in the United States: Expert Review

BEST PRACTICE ADVICE 1: There are identifiable high-risk groups in the United States who should be considered for GC screening. These include first-generation immigrants from high-incidence GC regions and possibly other non-White racial and ethnic groups, those with a family history of GC in a first-degree relative, and individuals with certain hereditary gastrointestinal polyposis or hereditary cancer syndromes. **BEST PRACTICE ADVICE 2:** Endoscopy is the best test for screening or surveillance in individuals at increased risk for GC. Endoscopy enables direct visualization to endoscopically stage the mucosa and identify areas concerning for neoplasia, as well as enables biopsies for further histologic examination and mucosal staging. Both endoscopic and histologic staging are key for risk stratification and determining whether ongoing surveillance is indicated and at what interval. **BEST PRACTICE**

Table 1. Risk Factors That Should Prompt Consideration of a Personalized Approach to Screening for Gastric Cancer in the United States Among Individuals 45 Years and Older

Risk factors
Early-generation immigrants from moderate to high incidence GC regions (defined as GC incidence ≥10–12 per 100,000 people; includes Eastern Europe, Andean Latin America, and East Asia)[a]
Family history of GC in a first-degree relative (to start 10 y earlier than the youngest affected relative)
Non-White racial and ethnic groups with established moderate to high incidence GC[a]
Personal history of chronic *Helicobacter pylori* infection and at least 1 of the following: • History of regularly smoking tobacco (>20 pack-years) • Chronic consumption of high-salt diet, red meat, processed meats, and foods • Individuals living under persistent poverty in the United States[b]
Certain hereditary GI polyposis syndromes and hereditary cancer syndromes

Gastroscopy for all BRCA carriers ?

- ~~Not really, d/t low GC rate in general population and RR of 1.5-2.5 in carriers~~
- Gastroscopy should be considered for all carriers at age 45-50y, with routine biopsies for OLGA / OLGIM
- Consider: origin, HP status, smoking, patient preference
- For ongoing screening – risk stratification based on endoscopic and histologic findings

Topics for decision

1. Gastroscopy for all BRCA carriers ? Protocol ?
2. Place of FH
3. Test and treat for HP ? When ?

Place of FH for GC in BRCA

- No data for increased risk specific for BRCA carriers
- Data for other hereditary syndromes for association of cancer and FH (e.g – colon in Lynch, breast / pancreas in BRCA)
- Very small fraction of BRCA carriers → low economic burden

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- Data for other hereditary syndromes for association of cancer and FH (e.g – colon in Lynch, breast / pancreas in BRCA)
- Very small fraction of BRCA carriers → low economic burden

- Recommendation: routine screening with biopsies at age 45-50y or 10y before family case, every 3y

Topics for decision

1. Gastroscopy for all BRCA carriers ? Protocol ?
2. Place of FH
3. Test and treat for HP ? When ?

Test and treat for HP

FOR

- ✓ Synergism between carrier-ship and HP infection
- ✓ Ease of testing
- ✓ Risk removal for GC

AGAINST

- ✓ Resistant strains
- ✓ SE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Helicobacter pylori, Homologous-Recombination Genes, and Gastric Cancer

Yoshiaki Usui, M.D., Ph.D., Yukari Taniyama, Ph.D., Mikiko Endo, B.Sc.,

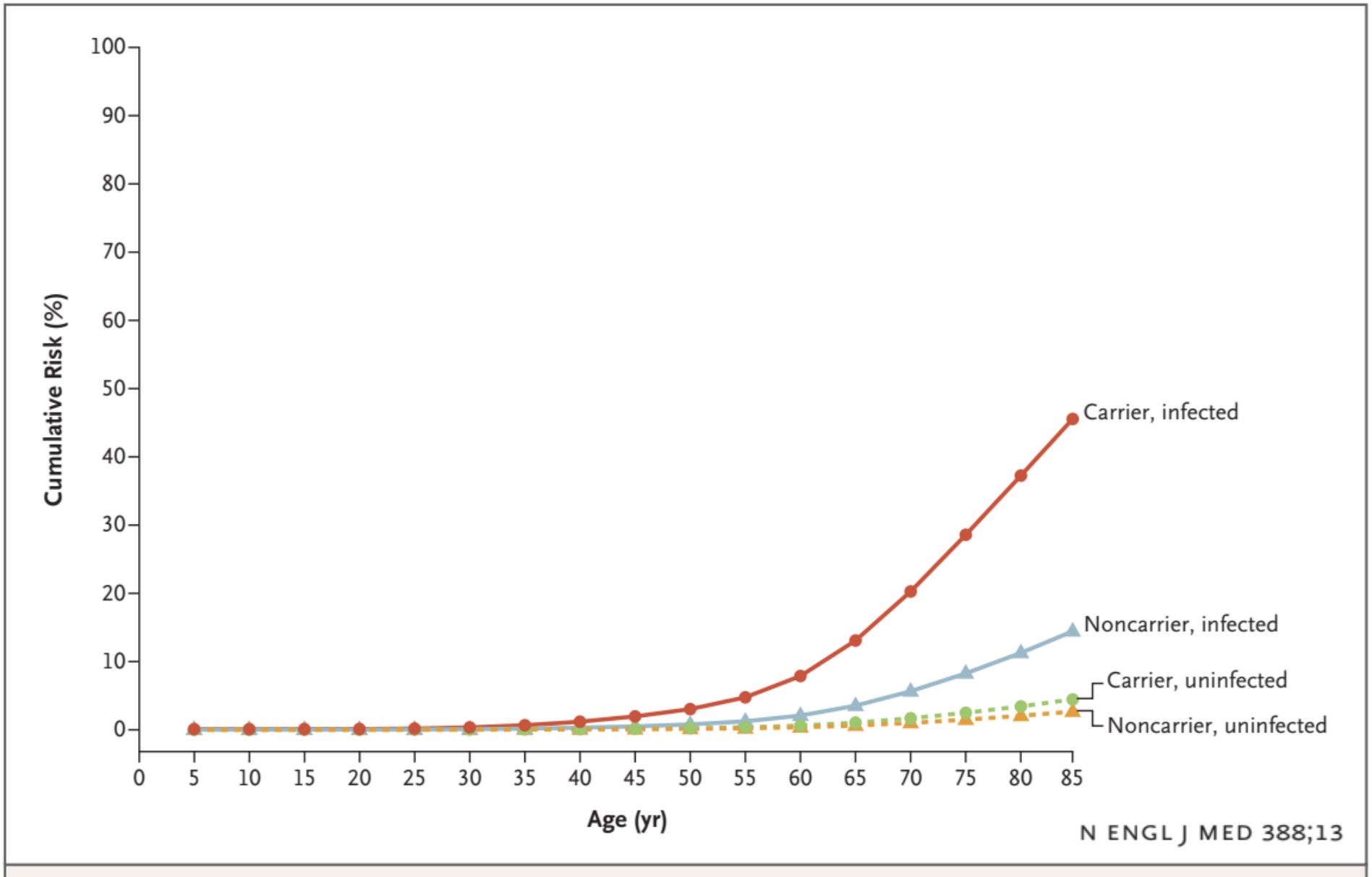
METHODS

We evaluated the association between germline pathogenic variants in 27 cancer-predisposing genes and the risk of gastric cancer in a sample of 10,426 patients with gastric cancer and 38,153 controls from BioBank Japan. We also assessed the combined effect of pathogenic variants and *H. pylori* infection status on the risk of gastric cancer and calculated the cumulative risk in 1433 patients with gastric cancer and 5997 controls from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC).

RESULTS

Table 3. Combined Effect of Germline Pathogenic Variants in Gastric Cancer Risk Genes and *H. pylori* Infection Status on the Risk of Gastric Cancer in HERPACC.*

Gene Category and *H. pylori* Status	Noncarriers†		Carriers		Relative Excess Risk Due to Interaction		Odds Ratio	
	No. of Patients/No. of Controls	Odds Ratio (95% CI)	No. of Patients/No. of Controls	Odds Ratio (95% CI)	Estimate (95% CI)	P Value for Additive Interaction	Estimate (95% CI)	P Value for Multiplicative Interaction
Overall gastric cancer risk genes‡								
H. pylori–negative	189/3173	1.00 (reference)	4/51	1.27 (0.45 to 3.59)	14.22 (2.50 to 25.93)	0.02	2.76 (0.84 to 9.04)	0.09
H. pylori–positive	1198/2745	5.76 (4.88 to 6.80)	32/21	20.25 (11.28 to 36.37)				
Homologous-recombination genes§								
H. pylori–negative	189/3173	1.00 (reference)	4/39	1.68 (0.59 to 4.83)	16.01 (2.22 to 29.81)	0.02	2.32 (0.69 to 7.81)	0.18
H. pylori–positive	1198/2745	5.76 (4.88 to 6.80)	30/18	22.45 (12.09 to 41.70)				
Mismatch-repair genes¶								
H. pylori–negative	189/3173	1.00 (reference)	0/7	NA	−0.67 (−10.55 to 9.22)	0.90	NA	NA
H. pylori–positive	1198/2745	5.76 (4.88 to 6.80)	1/2	4.09 (0.36 to 45.99)				


Cumulative Risk (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
Age (yr)
Carrier, infected
Noncarrier, infected
Carrier, uninfected
Noncarrier, uninfected
N ENGL J MED 388;13

ORIGINAL ARTICLE

Helicobacter pylori, Homologous-Recombination Genes, and Gastric Cancer

Yoshiaki Usui, M.D., Ph.D., Yukari Taniyama, Ph.D., Mikiko Endo, B.Sc.,

tor protein.[29] Most *H. pylori* strains isolated in East Asia (up to 96.3%) are CagA-positive.[30] Imai et al. showed that *H. pylori* CagA, both Western and East Asian types, elicits features similar to those seen in *BRCA*-mutated cells: DNA double-strand breaks and a disabling of error-free DNA repair mediated by homologous recombination, which contribute to gastric carcinogenesis.[23] We hypothesize that the gastric carcinogenesis–related DNA damage due to *H. pylori* infection is enhanced in persons with a reduced DNA damage-repair capacity due to damaging variants in the homologous-recombination genes. The cumulative

Test and treat for HP

AGA Clinical Practice Update on Screening and Surveillance in Individuals at Increased Risk for Gastric Cancer in the United States: Expert Review

Shailja C. Shah,[1,2] Andrew Y. Wang,[3] Michael B. Wallace,[4] and Joo Ha Hwang[5]

Opportunistic *H pylori* Screening and Eradication as an Essential Adjunctive Strategy for Gastric Cancer Prevention

Best Practice Advice 4: *H pylori* eradication is essential and serves as an adjunct to endoscopic screening and surveillance for primary and secondary prevention of GC. Opportunistic screening for *H pylori* infection should be considered in individuals deemed to be at increased risk for GC (refer to Best Practice Advice 1). Screening for *H pylori* infection in adult household members of individuals who test positive for *H pylori* (so-called "familial-based testing") should also be considered.

H pylori is the most common infectious carcinogen worldwide and is responsible for 90% of the global GC

ecommendation: test and treat

r HP at the time of diagnosis

Summary of recommendations

- Gastroscopy should be considered for all carriers at age 45-50y, with routine biopsies for OLGA / OLGIM
- For ongoing screening – risk stratification based on endoscopic and histologic findings
- FH - routine screening with biopsies at age 45-50y or 10y before family case, every 3y
- Test and treat for HP at the time of diagnosis