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Commentary

Helicobacter pylori, BRCA Pathogenic Germline Variants, and Gastric Cancer

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Introduction

Every day, family medicine, primary care and internal medicine clinicians are responsible for advising their patients who have common gastrointestinal symptoms whether to undergo screening for Helicobacter pylori, which affects more than one-half the world's population and is considered the most common bacterial infection [1]. Also, for patients who carry the most common inherited cancer predisposing genes, BRCA 1 and BRCA 2 pathogenic germline variants (PGVS), those clinicians provide tests and referrals to specialists for recommended screening for the currently considered BRCA-associated cancers [2].

According to the World Health Organization, gastric cancer (GC) was the fourth leading cause of cancer deaths globally in 2020 [3]. The most prevalent risk factor for GC is Helicobacter pylori infection [1,4]. In fact, 90% of GC cases not involving the gastric cardia are associated with H. pylori [1,4]. In the United States, the Standard of Care for which screening tests are recommended for BRCA PGV carriers is provided in the National Comprehensive Cancer Network (NCCN) guidelines, which currently recommend that BRCA PGV carriers should be screened for BRCA-associated cancers (e.g., breast, ovarian, pancreatic, prostate cancers) [2]. Currently, GC is not considered a BRCA-associated cancer [2].

Recent studies demonstrated that BRCA PGV carriers with untreated H. pylori infection have a remarkably high risk of developing GC [5,6]. In this commentary, the rationale for considering GC screening for all BRCA PGV carriers is discussed. Also discussed is whether BRCA PGV carriers found to have H. pylori should be referred for GC screening. Screening patients infected with H. pylori could result in diagnosing more GCs at earlier, more curable stages. Eradicating H. pylori will hopefully mitigate the high risk of GC developing in BRCA PGV carriers.

Evidence that BRCA PGVs are GC-predisposing

Although variable designs of the many published studies limit the certainty for concluding that BRCA PGVs are GC-predisposing, the preponderance of evidence suggests that BRCA PGV carriers are at increased risk for developing GC, albeit the lifetime likelihood of developing GC (i.e., penetrance) for the average BRCA PGV carrier does not appear nearly as high as their lifetime risk for developing other established BRCA-associated cancers, such as breast (49% and 57%, BRCA1 and BRCA2, respectively) or ovarian cancer (40% and 18%, BRCA1 and BRCA2, respectively) [7].

For example, a meta-analysis reported by Lee et al showed that the gastric cancer relative risk among BRCA1 carriers was numerically but not statistically significant [8]. However, in a recent, very thorough review, Buckley et al summarized numerous trials showing that BRCA1 PGV carriers do have an increased relative risk of developing GC (compared to a general population cohort) [9]. The authors cite one study in which the relative risk was over 2-fold greater among close to 9000 BRCA1 PGV carriers compared to the general population risk and Brose et al reported that, compared to a general population cohort, BRCA1 PGV carriers had age adjusted risks for developing GC of 5.5% and 0.8% (95% CI 3.4-7.5), respectively [10,11].

Although Buckley et al also cited limited data suggesting no increased GC risk from BRCA2 PGVs, they noted five studies that demonstrated an increased relative GC risk among BRCA2 PGV carriers, again compared to a general population cohort [9]. For example, in their multinational study, Li et al demonstrated a GC relative risk of 3.69 for BRCA2 PGV carriers. (10) In their meta-analysis of BRCA2 PGV GC risk, Lee et al showed a relative GC risk of 2.15 for BRCA2 carriers (95% CI 1.98-2.33) [8].

Buckley et al concluded "Despite the handful of studies to the contrary, the constellation of evidence cited above, highlighted by the 2021 meta-analysis by Lee et al and 2022 studies by Li et al and Momozawa, strongly suggest that BRCA2 PV carriers are at increased risk for GC" [9].

Identifying BRCA PGV carriers

The NCCN Guidelines are "the recognized standard for clinical direction and policy in cancer care" and are essential to "better inform the decision-making process between patients and physicians, ultimately improving patient outcomes." [12]. The NCCN guidelines almost exclusively only suggest germline testing (GT) for those patients estimated to have high pre-

test probabilities of harboring a BRCA PGV [2].

Recently, a number of articles have demonstrated a high likelihood of BRCA PGVs in patients with common cancers not typically considered BRCA-related. For example, from a cohort with esophageal, gastric, and gastroesophageal cancers (n=96) Uson et al showed that 15% of patients carried PGVs, and BRCA1 and BRCA2 were among the most common PGVs identified [13]. Sorscher et al showed that 14.9 % of patients diagnosed with lung cancer (n= 7,788) carry a PGV and the most common PGV identified was BRCA2 [14]. Coughlin et al showed that among individuals diagnosed with colorectal cancer (n=34,244) 1% had a BRCA1 or BRCA2 PGV [15].

These results suggest that many patients with BRCA PGVs are not being screened for those PGVs prior to the time their apparent non-BRCA-associated cancers are diagnosed. Notwithstanding the reasons that patients with currently classified non-BRCA-related cancers are not tested before their diagnoses of those non-BRCA-related cancers, thousands of those patients and their family members are being denied the opportunities afforded by GT and then following the recommended measures for those identified as BRCA PGV carriers.

For example, per the NCCN guidelines, it is recommended that patients with BRCA PGVs at some point undergo bilateral salpingo-ophorectomy surgery which is proven to mitigate their risk of developing breast cancer [2]. In patients who decline bilateral mastectomy for prevention, regular breast MRIs are recommended for earlier detection. The NCCN also recommends that BRCA PGV carriers should be considered for pancreatic cancer screening [2].

Recognizing the disparities in who is offered GT testing, President Biden's Moonshot 2.0 Initiative recommended that essentially all patients diagnosed with solid tumor malignancies be evaluated for GT [16]. If this policy is adopted, without also offering universal GT, the disparities between socioeconomic groups in who undergoes GT will likely expand because, as is currently the case, only those who can afford to pay out of pocket will undergo GT, and most patients with diagnosed cancer currently do not meet guidelines' criteria for testing.

H. pylori and BRCA-related Gastric Cancer

A particularly compelling reason to recognize BRCA as GC predisposing is because several recent studies suggest that although BRCA PGVs may not be associated with GC penetrance high enough to justify including GC as a BRCA-associated cancer, those individuals with BRCA PGVs and infected with H. pylori carry a very high risk of developing GC [5,6].

H. pylori is the most common bacterial infection in humans [17]. In fact, in their 2018 comprehensive review, Hooi et al estimated that there were 4.4 billion individuals with H. pylori infections worldwide in 2015 and estimated the North American prevalence to be 37.1% [1].

The lifetime risk of GC among those with BRCA PGVs is reportedly less than 5% among those not infected with H. pylori [10]. However, Usui et al recently reported that patients with tumors with homologous-recombination gene PGVs (e.g., BRCA) have a 45.5% lifetime risk of developing GC [5].

Also, in a New England Journal of Medicine article, Choi et al reported a randomized, placebo-controlled trial that demonstrated that GC incidence was reduced by eradicating H. pylori in patients with first degree relatives who had been diagnosed with GC [6]. There were 2.9% and 0.8% incidences of GC over a median follow-up period of 9.2 years in those with eradicated and those with persistent H. pylori infections, respectively. Although Choi et al did not specifically evaluate the elimination effect in BRCA carriers, based on the reports by Usui et al and Choi et al, it seems reasonable to consider patients identified as BRCA PGV carriers for H. pylori testing and eradication of H. pylori if it is identified [5,6]. It is important to recognize that different strains of H. pylori have different regional prominence and virulence in promoting GC [1,14,18].

Current guidelines vary in recommendations for which patients should be screened for H. pylori. The United States Preventive Services Task Force (USPSTF) drafted guidelines in 2022, but later decided to not offer formal guidelines [19]. Lamont reviewed different H. pylori screening guidelines and concluded that there was evidence to include "uninvestigated dyspepsia" as an indication for GT. Following that recommendation, along with more firmly established guideline recommendations for H. pylori testing, should translate into a sizable proportion of patients in internal medicine, primary care and family medicine clinics being screened for H. pylori [20]. For example, studies outside the U.S. suggest that roughly 5-7% of primary care level consults are for dyspepsia [21,22].

Also, patients eligible for GT for BRCA PGVs have been expanding dramatically, including the NCCN recommendation that all patients diagnosed with ovarian, pancreatic and prostate cancer and a large proportion of patients diagnosed with colorectal or breast cancer should be screened for BRCA PGVs [23]. Of the roughly 18.1 million cancer survivors living in the U.S., the most common cancer-predisposing gene they carry is either BRCA1 or BRCA2 and many of these patients are followed exclusively by family medicine, primary care or internal medicine clinicians [24]. When a BRCA PGV is identified, GT is recommended for first degree relatives. Thus, internists are frequently responsible for screening for H. pylori and arranging screening tests for BRCA-related cancers in patients and family members identified as BRCA PGV carriers.

Conclusions

In "Gastric Cancer Risk and Pathogenesis in BRCA1 and BRCA2 Carriers" Buckley et al recommended that "discussion of the potential merits of surveillance and other strategies for GC risk management is certainly warranted by the organizations that develop and implement guidelines (e.g., NCCN), and GC risk should be addressed in future guideline iterations" [9]. In the meantime, Buckley et al recommend H. pylori testing for BRCA PGV carriers, inclusion of GC screening among BRCA carriers at the time of their recommended pancreatic cancer screening, and "low threshold" for upper endoscopy screening among patients with upper GI symptoms that suggest the possibility of GC.

Despite the meta-analyses cited above, the fairly low penetrance suggests that additional epidemiologic and other studies are likely needed before BRCA PGVs will considered GC-predisposing. Expanding the guidelines for H. pylori testing to include BRCA PGV carriers might identify patients for whom H. pylori eradication could have profound benefits by reducing GC risk. Also, given the high risk of GC in BRCA PGV carri-

ers infected with H. pylori, it seems reasonable to refer these patients for consultations to discuss GC screening.

Conflict of Interest: Dr. Sorscher was formerly, briefly employed by Invitae, Corp.

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