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Glucose-6-phosphate dehydrogenase deficiency and risk of colorectal cancer in Northern Sardinia

A retrospective observational study

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency has been associated with a lower cancer risk, possibly via a reduction of mutagenic oxygen-free radicals and by reducing nicotinamide–adeninedinucleotide–phosphate for replicating cells. In Sardinia, the enzyme defect is frequent as a consequence of selection by malaria in the past. This study investigated the relationship between G6PD deficiency and colorectal cancer (CRC).

A retrospective case-control study of 3901 patients from Sardinia, who underwent a colonoscopy between 2006 and 2016, was performed. G6PD phenotype was assessed for each subject. The proportion of pre and malignant colorectal lesions was compared in cases (G6PD-deficient) and controls (G6PD-normal). Data concerning age, sex, family history of CRC, smoking habits, body height, and weight, and also associated diseases were collected.

The CRC risk reduction was 43.2% among G6PD-deficient compared with G6PD-normal subjects (odds ratio 0.57, 95% confidence interval 0.37–0.87, $P=0.010$). Age, sex, family history of CRC, and also comorbidities such as type 1 diabetes and ischemic heart disease, were significantly associated with CRC risk. The protective effect of G6PD deficiency remained significant after adjusting for all covariates by logistic regression analysis, and was consistently lower across all age groups.

Glucose-6-phosphate dehydrogenase enzyme deficiency is associated with a reduced risk of CRC.

Abbreviations: BMI = body mass index, CI = confidence interval, CRC = colorectal cancer, G6PD = glucose-6-phosphate dehydrogenase, IBD = inflammatory bowel disease, OR = odds ratio.

Keywords: association study, colorectal cancer, glucose-6-phosphate dehydrogenase deficiency

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide; however, incidence and mortality vary according to geographical area and population. CRC rate differences are related to dietary and environmental exposures, and to genetic factors.[1] It is currently believed that most CRCs develop with recognizable histologic changes that include adenomatous polyps. Adenomas are considered premalignant lesions, and the progression to cancer is slow, providing a wide window of time for cancer prevention or diagnosis while still at a curable stage. There are numerous options available to detect pre or cancerous polyps including flexible sigmoidoscopy,[2] colonoscopy,[3] computed tomography colonography,[4] faecal occult blood,[5] the newer stool DNA test,[6] and, more recently, the noninvasive technique tissue resonance interaction method (TRIMprob).[7]

Experts currently recommend choosing a testing strategy based on patient preferences while taking into consideration factors that may increase or decrease the CRC risk. The major conditions that dramatically increase the risk to develop CRC are rare inherited genetic disorders such as familial adenomatous polyposis,[8] hereditary nonpolyposis colon cancer,[9] and inflammatory bowel disease (IBD).[10] Other known factors associated with an increased risk of CRC are a personal or family history of CRC or polyps, sex, and age.[1] Lifestyle factors also influence the risk including diets low in fruit and vegetables and rich in saturated fat, and red or processed meat, obesity, smoking habits, alcohol consumption, and sedentary lifestyle. Hypothesized protective factors include regular physical activity,[11] a diet rich in fiber,[12] and use of aspirin and nonsteroidal anti inflammatory drugs.[13]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is among the genetic factors hypothesized to protect from colorectal carcinogenesis. G6PD is a cytoplasmic enzyme able to catalyze the first step of the pentose phosphate pathway, which plays a key role in producing the extramitochondrial coenzyme nicotinamide adenine dinucleotide phosphate (NADPH), and also the ribose, needed to synthesize DNA.[14] The G6PD gene maps on the long arm of X chromosome (Xq28 locus), and more than 140 loss-of-function mutations have been identified as being responsible for

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enzyme deficiency.[15] G6PD deficiency is one of the most common inherited enzyme defects. It is widespread in tropical and subtropical areas such as sub-Saharian Africa, and also in the Mediterranean area. In the island of Sardinia, the overall prevalence of G6PD deficiency ranges between 12% and 24%, and in most cases is due to the G6PD *Mediterranean* variant (a C→T transition at nucleotide 563).[16] This variant is estimated to have arisen between 1500 and 6700 years ago.[17] The majority of G6PD-deficient individuals remain asymptomatic; however, they may experience acute hemolytic anemia upon exposure to *Vicia faba*, infections, and a variety of drugs. Because of X-linkage, G6PD deficiency is always fully expressed in men (hemizygotes) and in homozygote women. The enzyme activity is mostly intermediate, in women heterozygote for the G6PD *Mediterranean* variant, although it varies greatly from normal-to-deficient range, as a result of possible skewing in X chromosome inactivation.[14]

In 1965, Beaconsfield et al[18] reported an inverse association between the geographic distribution of G6PD deficiency and cancer, and more specifically for CRC. In addition, a lower cancer prevalence compared with the rest of Europe, where G6PD deficiency is uncommon, was reported in Sardinia by Sulis.[19] Further, large epidemiological studies conducted in Sardinia between 1980s and 1990s supported an inverse relationship between G6PD deficiency and lower cancer mortality in men.[20,21] However, additional investigations yielded inconclusive results.[22–24] After more than half a century of research, the hypothesis of a negative correlation between G6PD deficiency and cancer susceptibility is still insufficiently supported by empirical evidence.

In this study, the hypothesis that G6PD deficiency may be "protective" against CRC was tested in a large cohort of Sardinian subjects who underwent colonoscopy.

2. Methods

This was a retrospective case-control study conducted in Northern Sardinia. Charts from inpatients and outpatients undergoing colonoscopy for any reason [screening, abdominal pain, surveillance programs, change in bowel habits, gastrointestinal (GI) alarm features], from January 2006 to January 2016, and a known G6PD status were collected. At the time of colonoscopy, each patient was interviewed by a gastroenterologist. A medical history was obtained comprising previously diagnosed diseases such as type 1 and 2 diabetes, ischemic heart disease, and also cholecystectomy. Demographic information including sex, age, smoking habits, anthropometric components (height and weight), and a family history of CRC were recorded in a computerized system.

In the case of multiple examinations for the same patient within the given time period, only the procedure corresponding to the first diagnosis of colonic premalignant or malignant lesion was considered.

Presence and number of lesions were assessed by a complete colonoscopy. According to the location, lesions were classified as colonic or rectal. Retrieved polyps, and also biopsies from suspected cancers and other mucosal abnormalities were sent for histological evaluation. Colonic tissue specimens were reviewed by an expert GI pathologist. Histology examination was considered the gold standard for colonic/rectal lesions. For patients undergoing colonoscopy in the postoperative or polypectomy surveillance programs, the age at first diagnosis of colon/rectal lesion was considered.

2.1. G6PD assay

Glucose-6-phosphate dehydrogenase activity was determined in all patients by a quantitative assay based on the ratio between G6PD/6GPD in erythrocytes, as previously reported and validated in other studies.[25,26] A ratio less than 0.1 was used to define the presence of G6PD enzyme deficiency and the results were expressed qualitatively as a dichotomous variable (positive/negative). No molecular analysis was performed in G6PD-deficient patients.

2.2. Ethical considerations

An Institutional Review Board approval was obtained from the local ethics committee (*Comitato di Bioetica, Azienda Ospedaliero Universitaria di Sassari*, Italy (Prot N° 3004/CE, 2016).

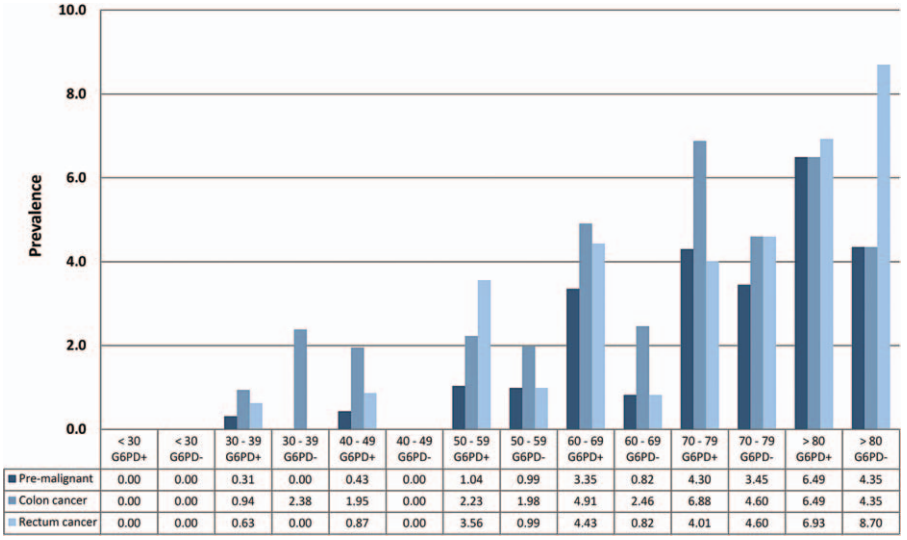
2.3. Statistical analysis

All patients were stratified by age in 10-year intervals, and the frequency distribution of CRC, including premalignant lesions, according to G6PD status, was calculated and expressed as a percentage. The association between each independent variable in the study and the prevalence of CRC was tested by calculating odds ratios (ORs) and their 95% confidence intervals (95% CIs) by the Mantel–Haenszel method. Frequencies were compared for categorical variables such as age, sex, G6PD status, smoking habits, family history for CRC, body mass index (BMI), and comorbidities. BMI was calculated by using the formula weight (kg)/height $(m)^2$. Obesity was defined as a BMI $\geq 30\,kg/m^2$. According to histological features, patients were classified as having adenomas (with low-grade dysplasia); advanced adenomas (with high-grade dysplasia or in situ carcinoma); and cancer.[7] The TNM classification of malignancies was not available from the charts.

The association between G6PD deficiency and CRC was tested by multiple logistic regression with a significance level P less than 0.05, while controlling for potential confounding covariates such as age, sex, family history, BMI, smoking habits, and comorbidities. For each covariate, the ORs and their 95% CIs by using the Wald formula ($95\%\ CI = OR^{1\pm fi/SE}$) were calculated. To avoid overfitting in final multivariable logistic model, resampling techniques were implemented to derive bias-corrected CIs. All statistical analyses were carried out using SPSS statistical software (version 16.0, Chicago, IL), and 2-sided P values lower than 0.05 were considered statistically significant.

3. Results

A total of 3901 charts of patients (60.9% women) who underwent colonoscopy were available for analysis, resulting in 452 patients with G6PD deficiency (cases) corresponding to 11.6%, and 3449 patients normal for G6PD (controls). The mean age of cases and controls was similar (57.7 ± 16 vs 57.5 ± 15 years; $P = 0.870$). G6PD enzyme deficiency was detected in 8.9% of men and in 13.3% of women. According to the colon site, prevalence of colon cancer was 4.2% (19/452) in cases and 7.1% (244/3901) in controls (OR 0.58, 95% CI 0.36–0.93, $P = 0.022$). For the rectum, the prevalence was also significantly lower, that is, 1.8% (8/452) in cases and 3.9% (133/3901) in controls (OR 0.45, 95% CI 0.22–0.92, $P = 0.025$). In Fig. 1, the prevalence of colorectal lesions according to age decades, colon site, and G6PD status is shown.



	< 30 G6PD+	< 30 G6PD-	30 - 39 G6PD+	30 - 39 G6PD-	40 - 49 G6PD+	40 - 49 G6PD-	50 - 59 G6PD+	50 - 59 G6PD-	60 - 69 G6PD+	60 - 69 G6PD-	70 - 79 G6PD+	70 - 79 G6PD-	> 80 G6PD+	> 80 G6PD-
Pre-malignant	0.00	0.00	0.31	0.00	0.43	0.00	1.04	0.99	3.35	0.82	4.30	3.45	6.49	4.35
Colon cancer	0.00	0.00	0.94	2.38	1.95	0.00	2.23	1.98	4.91	2.46	6.88	4.60	6.49	4.35
Rectum cancer	0.00	0.00	0.63	0.00	0.87	0.00	3.56	0.99	4.43	0.82	4.01	4.60	6.93	8.70

Figure 1. Prevalence of premalignant colorectal lesions, colon cancer, and rectum cancer according to age decades and G6PD status (G6PD+: G6PD-normal; G6PD−: G6PD deficiency). G6PD = glucose-6-phosphate dehydrogenase.

The overall prevalence of malignancy, including adenocarcinoma and high-grade dysplasia/carcinoma in situ, in cases and controls across age decades, is shown in Table 1. As expected, colorectal malignancies were more frequent among the oldest patients. However, CRC was less frequent among cases compared with controls for each age decade (Table 1). Interestingly, among cases, a remarkable reduction of colorectal malignancies was observed in patients younger than 50 years of age compared with controls (1/118 vs 21/990; OR 0.39, 95% CI 0.05–2.96, $P = 0.348$). According to literature, a family history of colon cancer was more frequent in CRC-positive (17%) compared with CRC-negative subjects (7.7%). Moreover, patients positive for colon malignancy and a family history of CRC were, on average, younger (less than 50 years of age) than those positive for colon malignancy, but negative for a family history of CRC (Table 2). Additional risk factors for CRC in our studied population were male sex, cigarette smoking, type 1 or type 2 diabetes, previous cholecystectomy, ischemic heart disease, and IBD (Table 2). Surprisingly, only a minimal difference of CRC prevalence was observed between obese and nonobese patients (Table 2).

The cumulative proportion of patients with CRC was 5.8% among cases and 9.5% among controls, respectively ($\chi^2 = 6.33$, $P < 0.0001$). Multiple logistic regression analysis is shown in Table 3. After adjusting for all covariates, G6PD deficiency remained associated with a 43.2% decreased risk for CRC (OR 0.568, 95% CI 0.371–0.872, $P = 0.010$), although the effect size was larger for age, male sex, family history, and comorbidities such as ischemic heart diseases and type 1 diabetes.

4. Discussion

The hypothesis of a protective effect of G6PD deficiency against the development of malignancies arose many decades ago and a number of epidemiological studies have tried to evaluate its plausibility. Many of the studies were conducted in Sardinia where the frequency of this hereditary condition is one of the highest in the world.[14,16,19,27–29] An ecological approach, adopted in early studies,[19,20,21,30] provided the first hint of the existence of an inverse relationship between G6PD deficiency and cancer risk. Subsequent investigations have been based on all cancer mortality in order to have a larger sample size of deaths.

Table 1

Unadjusted odds ratio and 95% confidence interval for colorectal cancer (CRC) and premalignant colon lesions among 3901 patients with and without glucose-6-phosphate dehydrogenase (G6PD) deficiency undergoing colonoscopy.

	Controls (G6PD-normal)		Cases (G6PD deficiency)		
Variable	CRC-negative	CRC-positive, n (%)	CRC-negative	CRC-positive, n (%)	OR (95% CI)
Age, y					
<30	230	0 (0.0)	33	0 (0.0)	—
30–39	313	6 (1.9)	41	1 (2.4)	1.27 (0.15–10.84)
40–49	447	15 (3.2)	44	0 (0.0)	—
50–59	628	46 (6.8)	97	4 (4.0)	0.56 (0.20–1.60)
60–69	729	106 (12.7)	117	5 (4.1)	0.29 (0.12–0.74)**
70–79	592	106 (15.2)	76	11 (12.6)	0.81 (0.42–1.57)
≥80	185	46 (19.9)	19	4 (17.4)	0.85 (0.27–2.61)
Total patients	3124	325 (9.4)	427	25 (5.5)	0.56 (0.37–0.86)**

CI = confidence interval, OR = odds ratio.
* $P < 0.05$.
** $P < 0.01$.

Table 2

Risk factors for colorectal cancer (CRC) and premalignant lesions in 3901 subjects.

Variables	Total tested	CRC-positive	ORs (95% CI)	*P*
Age, y				
<30	263	0 (0.0%)	n/a	n/a
30–39	361	7 (1.9%)	Reference	—
40–49	506	15 (3.0%)	1.54 (0.62–3.83)	0.344
50–59	775	50 (6.5%)	3.49 (1.57–7.77)	0.001
60–69	957	111 (11.6%)	6.64 (3.06–14.39)	<0.0001
70–79	785	117 (14.9%)	8.86 (4.09–19.20)	<0.0001
≥80	254	50 (19.7%)	12.39 (5.52–27.85)	<0.0001
Sex				
Women	2377	172 (7.2%)	Reference	—
Men	1524	178 (11.7%)	1.66 (1.34–2.07)	<0.0001
Smoking habits				
No smoking	3109	250 (8.0%)	Reference	—
Smoking	792	98 (12.3%)	1.61 (1.26–2.07)	<0.0001
G6PD status				
Normal	3449	325 (9.4%)	Reference	—
Deficiency	452	25 (5.5%)	0.56 (0.37–0.86)	0.006
Family history				
No	3382	262 (7.8%)	Reference	—
Yes	519	88 (17.0%)	2.43 (1.87–3.16)	<0.0001
BMI, kg/m^{2*}				
<30	3401	289 (8.5%)	Reference	—
≥30	498	47 (9.4%)	1.12 (0.81–1.55)	0.485
Comorbidity				
None	3265	258 (7.9%)	Reference	—
T1D	11	3 (27.3%)	4.37 (1.15–16.58)	0.018
T2D	401	50 (12.5%)	1.66 (1.20–2.29)	0.002
Colecystectomy	137	20 (14.6%)	1.99 (1.22–3.26)	0.005
IHD	87	19 (21.8%)	3.26 (1.93–5.50)	<0.0001
IBD	222	1 (0.45%)	0.05 (0.01–0.38)	<0.0001

Patients positive for colon malignancy and a family history of CRC were, on average, younger (less than 50 years of age) than those positive for colon malignancy, but negative for a family history of CRC. CI = confidence interval, G6PD = glucose-6-phosphate dehydrogenase, IBD = inflammatory bowel disease, IHD = ischemic heart disease, OR = odds ratio, T1D = type 1 diabetes mellitus, T2D = type 2 diabetes mellitus.

* Body mass index (kg/m^2) for 2 patients the BMI was not available (2 missing data).

Studies targeted to site-specific cancers have been less frequent. The present investigation in a large population from Sardinia used a highly sensitive and specific assay,[25,26] and both premalignant and malignant colorectal lesions were included in the analysis. The study also controlled for a number of risk factors such as sex, age, smoking habits, BMI, family history of CRC, and associated diseases.

Data analysis showed statistically significant differences between the cumulative proportion of subjects who developed colorectal lesions among G6PD-deficient compared with non-deficient subjects, with a strong positive trend toward older ages. More specifically, a 43% reduction of OR for colorectal malignancies in G6PD-deficient carriers was observed, and this reduction was higher in subjects younger than 50 years of age. In addition, a lower prevalence of premalignant lesions was observed among cases. Multivariate analysis confirmed that the reduction of CRC risk in carriers of G6PD deficiency remained significant after adjusting for a number of covariates, although its effect size was lower than older age, male sex, and comorbidities such as ischemic heart disease and type 1 diabetes. Unexpectedly, in our cohort, BMI and cigarette smoking had a limited influence on CRC prevalence. Because only 14 patients had a BMI ≥40 kg/m^2, this may have likely lessened the effect of weight on CRC. Cigarette smoking has been associated with increased incidence and mortality from CRC. Our results confirm a 23% increase in the CRC risk among smokers, although no longer significant after adjusting for all covariates. A history of type 1 diabetes was associated with a higher risk of CRC probably due to the tumorigenic effect of insulin treatment, as previously reported.[31,32] Also ischemic heart disease was found to be associated with an increased CRC risk by 26% in multivariate analysis, indicating that both conditions might share a number of predisposing factors.[33]

The protective effect of G6PD on CRC was remarkably higher in our study than in previous studies, likely due to differences in design, sample size, age of participants, and accuracy of G6PD detection assay.[21,22,24,30]

Several potential explanatory factors have been proposed in the literature as biological mechanisms for decreased cancer risk among carriers of G6PD deficiency. Among these, a chronic NADPH deficiency induced by inhibition of pentose phosphate pathway was suggested.[14] Colon cancer cells in vitro are dependent on NADPH necessary for cholesterol and fatty acid biosynthesis required for proliferation.[34,35] NADPH shortage due to G6PD defects may reduce the production of superoxide anion and other free radicals such as nitric oxide,[36] which favor cancerogenesis by increasing the DNA mutation rate and the synthesis of proinflammatory cytokines.[37] Interestingly, decreased cancer cell proliferation was recently confirmed by using siRNAs against G6PD.[38] Finally, it is possible that the association between G6PD deficiency and development or progression of CRC could be actually due to an X-linked gene close to G6PD rather than a functional consequence of enzyme deficiency itself. Genes involved in colon cancer have been

Table 3

Multiple logistic regression analysis for G6PD status and other variables potentially associated with the risk of colorectal cancer.

Covariates	ORs	95% CI of ORs	*P*
G6PD status			
Normal	1.000	—	—
Deficiency	0.568	0.371–0.872	0.010
Age, y			
<50	1.000	—	—
≥50	6.281	4.030–9.791	<0.0001
Sex			
Women	1.000	—	—
Men	1.650	1.310–2.077	<0.0001
Family history			
No	1.000	—	—
Yes	2.788	2.118–3.669	<0.0001
BMI, kg/m^2			
<30	1.000	—	
≥30	0.902	0.620–1.314	0.592
Smoking			
No	1.000	—	—
Yes	1.234	0.886–1.719	0.213
Comorbidities			
None	1.000	—	—
T1D	4.271	1.018–17.92	0.047
T2D	1.249	0.895–1.742	0.191
Cholecystectomy	1.593	0.958–2.647	0.073
IHD	2.394	1.393–4.113	0.002

BMI = body mass index, CI = confidence interval, G6PD = glucose-6-phosphate dehydrogenase, IHD = ischemic heart disease, OR = odds ratio, T1D = type 1 diabetes mellitus, T2D = type 2 diabetes mellitus.

identified in regions of the X chromosome close to G6PD gene.[39,40]

Although our study displays several strengths, a number of limitations need to be taken into consideration. First, the cohort investigated was not representative of the general Sardinian population, but was referred to a GI section to undergo colonoscopy for any reason. A detailed distribution of potential confounders between normal and G6PD-deficient patients was not entirely assessed. However, the overall frequency of G6PD in our cohort is very close to the average frequency found in previous studies in the Sardinian population, so that under or overestimation of the enzyme defect in the study participants is unlike.

Other limitations of the study are the lack of detailed data regarding other risk factors or comorbidities usually associated with CRC, including diet composition, level of physical activity, medications, and so on.

5. Conclusions

In conclusion, the results of our study indicate that the loss of function of a housekeeping enzyme such as G6PD can delay or reduce the risk to develop CRC, and is consistent with the emerging hypothesis that G6PD has a broader and important biological role than previously thought. Further investigations are needed to fully understand the relationship between G6PD deficiency and CRC.

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