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Association of *CHEK2* I157T and *SULT1A1* R213H genetic variants with risk of sporadic colorectal cancer in a sample of Egyptian patients

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Abstract

Background: Recent research proposed an association between functional defects involving *CHEK2* I157T and *SULT1A1* R213H variants and increased incidence of several types of cancer. A total of 86 unrelated colorectal cancer patients attending the Surgical Oncology Department were recruited in the study. The second group of 152 healthy age- and sex-matched volunteers were included as controls. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) was applied for genotyping. Chi-square test was applied to compare genotype and allele frequencies in the studied groups. The purpose of the present study was to evaluate the association between *CHEK2* I157T and *SULT1A1* R213H polymorphisms and colorectal cancer.

Results: No significant differences in genotypes were detected between cases and controls in the present study for both *CHEK2* I157T and *SULT1A1* R213H polymorphisms ($\chi^2 = 1.839$; $P = 0.399/\chi^2 = 2.831$; $P = 0.243$), respectively. Likewise, discrepancies in allele frequency for the wild-type or mutant alleles were non-statistically significant in *CHEK2* I157T and *SULT1A1* R213H ($\chi^2 = 1.231$; $P = 0.267/\chi^2 = 0.180$; $P = 0.671$), respectively.

Conclusions: Results of the current study propose that *CHEK2* I157T and *SULT1A1* R213H polymorphisms are not associated with CRC development in Egyptian population. Further future studies on the functional implications of these polymorphisms are strongly recommended.

Keywords: Colorectal cancer, Polymorphism, *CHEK2*, *SULT1A1*

Background

Colorectal cancer (CRC) ranks third among the most frequent cancers and the fourth most common etiology of global cancer fatalities. CRC has become a leading health problem based on the fact that new CRC cases diagnosed yearly exceed a million worldwide and death represents the outcome in more than 30% of them [1]. Nowadays, CRC is considered in many countries as a major community health burden. Therefore, understanding the etiologies of this cancer is an area of extreme importance.

CRC development is a complex process involving the interplay between many factors. Both gene mutation and environmental factors have a crucial role in CRC development [2].

A multitude of evidence highlights the crucial genetic role in CRC risk [2]. Multiple reports concluded that inherited factors affect DNA repairing capacity which may result in cancer development [3–5]. Hence, subjects with hereditarily impaired DNA repairing capability are usually related to increased cancer risks [6, 7].

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The Checkpoint kinase 2 (*CHEK2)* gene is recognized as a breast cancer susceptibility gene [8], and multiple germ-line variants may be associated with an increased risk of colorectal, prostate, thyroid, and renal cancer in certain populations [9, 10]. *CHEK2* encodes the human homologue of the CDP-diacylglycerol synthase 1 (Cds1) and RADiation sensitive (RAD53) checkpoint kinases and serves a crucial role in DNA damage checkpoint pathway. Following DNA damage exacerbated by ionizing radiation, *CHEK2* activation is triggered by the ataxia-telangiectasia mutated (ATM) protein and thereafter, phosphorylates multiple substrates, including p53, Breast cancer type 1 susceptibility protein (BRCA1), Mouse Double Minute 2(Mdm2), Cell division cycle 25 A (Cdc25A), and Cell division cycle 25 C (Cdc25C), causing activation of DNA repairing pathways, cell cycle arrest, or apoptosis. Activated Chk2 was detected in early precursor specimens of urinary bladder, lung, breast, and colorectal carcinoma (but not in normal specimens) before genomic instability occurs and hence malignant transformation [11], raising a suggestion that DNA damage checkpoints are activated early in tumorigenesis stages. Hence, *CHEK2* mutations, or other genes involved in the ATM-CHEK2-p53 pathway, may permit tumorigenic cells evasion of normal cell cycle checkpoints, causing aberrant cell proliferation and survival, decreased genomic stability, and eventually, tumor progression [12].

Heterozygosity of I157T (rs17879961) in *CHEK2* gene that results in the substitution of an isoleucine (Ilu) for a threonine (Thr) is shown to reduce the functional pool of CHEK2 protein by forming heterodimers with the wild type [13] leading to impaired binding to BRCA1, CDC25A, and p53. As I157T is localized in a functionally important domain of *CHEK2*, and the protein with this mutation has been proven deficient in its ability to bind p53 and BRCA1 and to bind and phosphorylate Cdc25A [14]. A functionally defective *CHEK2* variant I157T was suggested to be associated with increased breast cancer risk, together with prostate cancer and a number of other cancers [9, 13, 15].

Sulfotransferases (*SULTs*) serve a crucial function in the normal physiological processes in addition to malignant transformation [16]. In humans, three members of the phenol sulfotransferase family exist (*SULT1A1*, *SULT1A2*, and *SULT1A3*). *SULT1A1* is expressed in the liver together with multiple extrahepatic sites like colon mucosa and plays a role in various xenobiotic detoxication pathways [17]. It serves a vital function in the metabolism and bioactivation of numerous environmental and dietary mutagenic factors, including heterocyclic amines involved in colorectal carcinogenesis together with various cancers [18]. Consequently, *SULT1A1* gene may represent a suitable candidate for genetic CRC studies. The *SULT1A1* gene resides on chromosome 16p12.1-p11.2 [19]. A polymorphism R213H(rs1042028) in the *SULT1A1* gene was recognized in the coding sector at nucleotide 638 (a G to A transition). This base replacement leads to amino acid sequential change from arginine to histidine (Arg213His), causing a reduction in enzyme activity [20].

The association between the genetic variants *CHEK2* I157T and *SULT1A1* R213H and colorectal cancer susceptibility still needs to be further explored. The aim of the present study was to evaluate the association between *CHEK2* I157T (rs17879961) and *SULT1A1* R213H (rs1042028) polymorphisms and CRC in an Egyptian population.

Methods

Population studied

The study was conducted on 86 sporadic unrelated (non-consanguineous) CRC patients attending the Surgical Oncology Department, from March 2018 to January 2019. The diagnosis and confirmation of colorectal cancer were done based on endoscopic and histopathological results. 152 healthy age- and sex-matched volunteers were recruited as controls. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics of research committee. Informed written consents were obtained from all participants after explanation of the purpose of the study.

History, clinical evaluation, and blood sampling

All participants were subjected to careful medical and family history taking. Data collected from CRC patients included tumor site, Dukes stage (stage A: limited to muscularis propria, stage B: extending beyond muscularis propria, stage C: nodes involved and stage D: distant metastatic spread) [21, 22] and tumor grade (well differentiated (low grade), moderately differentiated (intermediate grade) and poorly differentiated (high grade)). Venous blood samples for the molecular analysis were collected in EDTA tubes from all patients and controls.

Molecular study

Genomic DNA was extracted from peripheral blood leukocytes by salting out technique [23]. The*CHEK2* gene polymorphism I157T (rs17879961)was investigated by Polymerase Chain Reaction (PCR) amplification of genomic DNA followed by Restriction Fragment Length Polymorphism (RFLP); according to the method previously reported by Cybulski et al. [24].

Amplification via Veriti Thermal Cycler (Applied Biosystems) was performed using the following primer sequences: 5'-ACCCATGTATCTAGGAGAGCTG-3'

(forward) and 5'-CCACTGTGATCTTCTATGTCT GCA -3' (reverse). The PCR reaction was performed in a total volume of 50 ul including 25 ul 2X PCR master mix (0.05 U/μL Taq DNA polymerase, reaction buffer, 4 mM MgCl2, 0.4 mM of each dNTP) (Thermo- scientific), 1uM each primer, 5 ug DNA and nuclease free water up to 50 ul. The PCR program included: An initial denaturing step of 4 min at 95 °C followed by 30 cycles of 94 °C for 30 s, 57 °C for 1 min for annealing, and 1-min elongation at 72 °C, with a final elongation step of 72 °C for 7 min. The PCR products were digested with pst1 restriction enzyme (fast digest) (Thermoscientific)according to the manufacturer's protocol. For the *SULT1A1* gene polymorphism R213H(rs1042028) genotyping, the same method was applied except for an annealing temperature of 55C with the following primers sequences: 5'- GGGTCTCTAGGA GAGGTGGC-3' (forward) and 5'- GCTGTGGTCCAT GAACTCCT-3' (reverse) [25].

The amplified segments were digested with Hha1 restriction enzyme (fast digest) (Thermoscientific) according to the manufacturer's instructions.

Analysis of rs17879961 and rs1042028 polymorphisms

The digested PCR products were resolved by electrophoresis on 3% agarose gel stained with ethidium bromide for 20 min at 200 V and were sized with reference to a 50-bp DNA ladder.

Statistical analysis

Data were analysed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov, Shapiro and D'agstino tests were used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Student t-test was used to compare two groups for normally distributed quantitative variables. Odd ratio (OR) was used to calculate the ratio of the odds and 95% Confidence Interval of an event occurring in one risk group to the odds of it occurring in the non-risk group. Regression analysis was applied to detect the most independent/ affecting factor for affecting cases. Significance of the obtained results was judged at the 5% level.

Results

A total of 86 sporadic unrelated CRC patients and 152 controls were recruited in this study. There was statistical difference between cases and controls regarding the smoking status ($^{MC}p < 0.001^{*}$). Among the CRC cases, 74.4% of patients suffered from colon cancer, 21.1% from rectal cancer and 3.5% with rectosigmoid cancer. Regarding histologic differentiation, 19.8%, 68.6%, and 11.6% of CRCs were classified as low grade, intermediate grade, and high grade, respectively. The Dukes A, B, C, and D stages were 0%, 1.2%, 2.3%, and 96.5%, respectively (Table1).

Table 1 Clinical characteristics of the study subjects ($n = 86$)

	No. (%)
Tumor site	
Rectum	19 (22.1%)
Colon	64 (74.4%)
Caecum	24 (27.9%)
Ascending colon	16 (18.6%)
Hepatic flexure	4 (4.7%)
Transverse colon	9 (10.5%)
Splenic flexure	4 (4.7%)
Descending colon	7 (8%)
Rectosigmoid	3 (3.5%)
Tumor grade	
Low	17 (19.8%)
Intermediate	59 (68.6%)
High	10 (11.6%)
Min.–Max	1.0–3.0
Median (IQR)	2 (1.0–3.0)
Dukes stage	
B	1 (1.2%)
C	2 (2.3%)
D	83 (96.5%)
Min.–Max	2.0–4.0
Median (IQR)	4.0 (2.0–4.0)

Table 2 Results of Hardy–Weinberg equilibrium analysis of rs17879961 genotypes among cases and control

rs17879961	Observed	Expected	χ^2	*P*
Cases (n = 86)				
TT (Thr/Thr)	28	32.0	3.372	0.066
TC (Thr/Ile)	49	40.9		
CC (Ile/Ile)	9	13.0		
Control (n = 152)				
TT (Thr/Thr)	63	66.4	1.559	0.212
TC (Thr/Ile)	75	68.1		
CC (Ile/Ile)	14	17.4		

If $P < 0.05$—not consistent with HWE

The allelic distribution of rs17879961 and rs1042028 polymorphisms were in Hardy–Weinberg equilibrium (HWE) among the cases and the control groups (Tables 2, 3). The genotype and allele frequencies for the two single nucleotide polymorphisms (SNPs) between the cases and the control group are shown in Table 4 and Figs. 1 and 2. No significant differences in genotypes were detected

Table 3 Results of Hardy–Weinberg equilibrium analysis of rs1042028 genotypes among cases and control

rs1042028	Observed	Expected	χ^2	*P*
Cases (n = 86)				
CC (Arg/ Arg)	35	38.4	2.811	0.093
TC (Arg/ His)	45	38.1		
TT (His/His)	6	9.4		
Control (n = 152)				
CC (Arg/ Arg)	73	71.8	0.190	0.662
TC (Arg/ His)	63	65.3		
TT (His/His)	16	14.8		

If $P < 0.05$—not consistent with HWE

between the cases and control in the present study for both rs17879961 and rs1042028 polymorphisms ($\chi^2 = 1.839$; $P = 0.399/\chi^2 = 2.831$; $P = 0.243$), respectively. Likewise, discrepancies in allele frequency for the wild-type or mutant alleles were non-statistically significant in rs17879961 and rs1042028 ($\chi^2 = 1.231$; $P = 0.267/\chi^2 = 0.180$; $P = 0.671$) respectively. No significant association was found between rs17879961 and rs1042028 and CRC susceptibility in different models (Table 5).

Logistic regression analysis showed that age, gender and smoking are risk factors for colorectal cancer (Table 6). No significant association was detected between rs17879961 and rs1042028 polymorphisms and various clinicopathologic parameters of CRC (Table 7).

Discussion

The CHEK2 is a serine/threonine protein kinase that plays a crucial role in DNA damage response and the regulation of cell cycle. CHEK2 protein consists of three functional domains: SQ/TQ cluster domain (SCD), forkhead associated (FHA) domain, and kinase domain. The SCD is a target for (auto)phosphorylation and is thus crucial for activation and regulation of CHEK2 functions. The FHA domain is in charge of substrate specificity of CHEK2 through phosphorylation dependent protein–protein interactions and plays a role in the activation process of CHEK2 [26]. The I157T (c.470T > C) (rs17879961) variant resides in a phosphopeptide recognition domain (FHA domain), whose normal function is to enable protein formation of homodimers as well as substrate binding. Protein FHA domain mutation has been shown to interfere with complex formation with key substrates—p53 and Cdc25A. Since its ability of dimer formation remains intact, *CHEK2* I157T has been postulated to reduce the pool of wild-type CHEK2 protein via a dominant-negative interaction [13]. *CHEK2* gene is evolutionarily conserved with few germline variants described. CHEK2 I157T, together with 1100delC, were originally recognized in Li-Fraumeni syndrome families and speculated to be the etiological factor of the disease. Other studies showed that such variants may exert their effects through low-penetrant, rather than high-penetrance multiorgan tumor-susceptibility alleles [27]. The distribution of *CHEK2* I157T among European populations appears quite heterogeneous which may be attributed to migration and founder effects. Its frequency is highest in Russia 7.6% [28] and Finland 5.3% [29] followed

Table 4 The genotype and allele distribution of rs17879961 and rs1042028 polymorphisms among cases and control

	Cases (*n* = 86)	Control (*n* = 152)	χ^2	*P*	OR (95% C.I)
rs17879961					
TT (Thr/Thr)®	28 (32.6%)	63 (41.4%)			Ref
TC (Thr/Ile)	49 (57%)	75 (49.3%)	1.747	0.187	1.470 (0.829–2.606)
CC (Ile/Ile)	9 (10.5%)	14 (9.2%)	0.585	0.446	1.446 (0.560–3.734)
Allele					
T	105 (61%)	201 (66.1%)	1.231	0.267	Ref
C	67 (39%)	103 (33.9%)			1.245 (0.84–1.83)
rs1042028					
CC (Arg/Arg) ®	35 (40.7%)	73 (48.0%)			Ref
TC (Arg/His)	45 (52.3%)	63 (41.4%)	1.985	0.160	1.490 (0.855–2.597)
TT (His/His)	6 (7.0%)	16 (10.5%)	0.223	0.637	0.782 (0.282–2.171)
Allele					
C	115 (66.9%)	209 (68.8%)	0.180	0.671	Ref
T	57 (33.1%)	95 (31.3%)			1.090(0.73–1.63)

® Reference type, χ^2 chi-square test, *MC* Monte Carlo

p: *p* value for comparing between the studied group

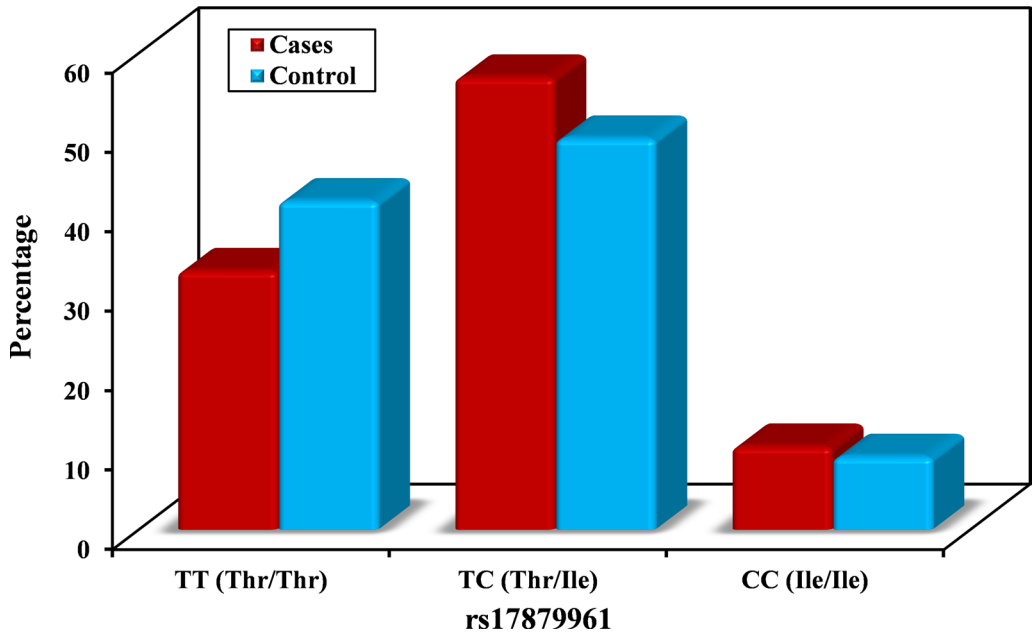

Fig. 1 The genotype distribution of rs17879961 polymorphisms among cases and control

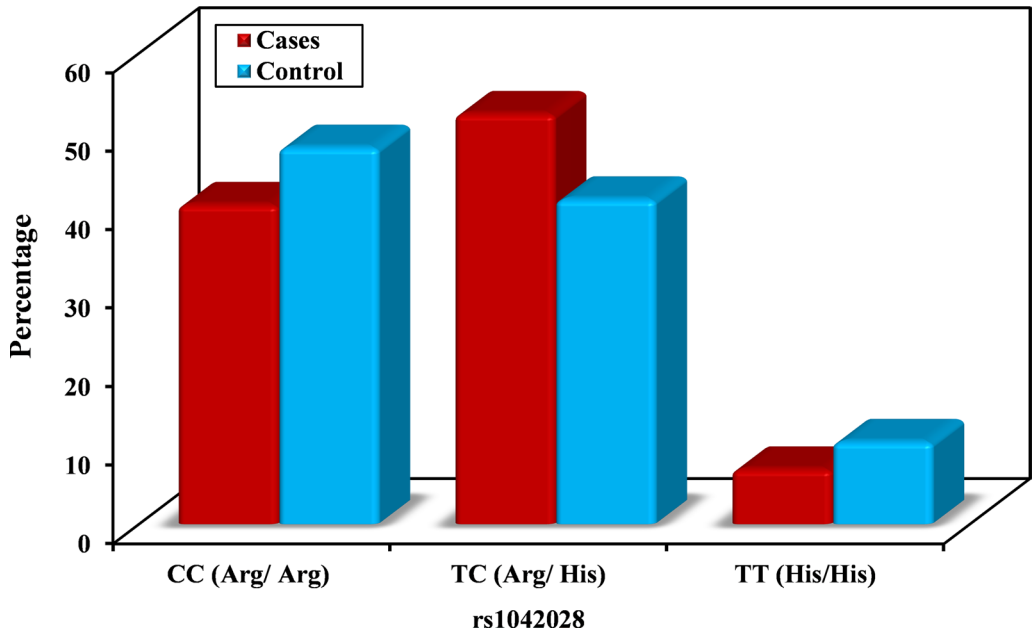

Fig. 2 The genotype distribution of rs1042028 polymorphisms among cases and control

by the Czech Republic 2.5% [28, 30]. In Italy it was not detected in any of 365 studied unrelated males [31]. In Germany, it was detected in 0.6% of controls and in Bella Russia in 1.3% [32]. Despite marked discrepancy in allele frequency, the variant has shown consistent association with CRC risk in various reports [9, 29, 33, 34]. In the present study, no association was detected between *CHEK2* I157T polymorphism and CRC risk, which is consistent Konstantinova et al. [35] who published his study on Bulgarian population, and was the first to report

Table 5 Association between rs17879961 and rs1042028 polymorphisms and CRC risk

	Cases (n = 86)	Control (n = 152)	P	OR (95% C.I)
rs17879961				
TC versus TT®	49/28	75/63	0.187	1.470 (0.829–2.606)
CC versus TT®	9/28	14 /63	0.446	1.446 (0.560–3.734)
Dominant: (CC + TC) versus TT®	58 /28	89/63	0.176	1.466 (0.842–2.553)
Recessive: CC versus (TC + TT) ®	9/77	14/138	0.753	0.868 (0.359–2.098)
Additive: TT® versus TC versus CC	28/49/9	63/75/14	0.234	1.290 (0.848–1.963)
rs1042028				
TC versus CC®	45 /35	63/73	0.160	1.490 (0.855–2.597)
TT versus CC®	6 /35	16 /73	0.637	0.782 (0.282–2.171)
Dominant model: (TT + TC) versus CC®	51/35	79/73	0.276	1.346 (0.789–2.299)
Recessive model: TT versus (TC + CC) ®	6/80	16/136	0.367	1.569 (0.590–4.171)
Additive model: TT versus TC versus CC®	6/45/35	16/63/73	0.664	1.095 (0.727–1.648)

® Reference type, χ^2 chi-square test, *MC* Monte Carlo

p: *p* value for comparing between the studied groups

*Statistically significant at $p \leq 0.05$

Table 6 Univariate and multivariate analysis for the parameters affecting colorectal cancer

	Univariate	#Multivariate		
	P	OR (95%C. I)	*P*	OR (95%C. I)
Sex (female)	< 0.001*	4.704 (2.635–8.398)	0.003*	4.034 (1.617–10.069)
Age (years)	< 0.001*	1.233 (1.169–1.301)	< 0.003*	1.229 (1.163–1.299)
Smoking	< 0.001*	0.268 (0.141–0.510)	0.066	0.410 (0.159–1.060)

OR odds ratio, *C.I* confidence interval

All variables with $p < 0.05$ was included in the multivariate

*Statistically significant at $p \leq 0.05$

a population in which *CHEK2* I157T does not increase CRC risk, although a very low penetrance effect could not be excluded.

The variation between the different studies may be attributed to ethnic discrepancies, differences in sample size, variability in the inclusion criteria, and the study techniques.

One study correlated *CHEK2* I157T with colon cancer tumor characteristics [29], but prevalence in any of the grade or stage subclassification was not detected. In the study conducted by Konstantinova et al. [35], no such prevalence was detectable. Instead, they reported a relation to two other tumor criteria—histological type

Table 7 Associations between rs17879961 and rs1042028 polymorphisms and clinicopathologic parameters of CRC

Cases (*n* = 86)	rs1042028			χ^2	MCp	rs17879961			χ^2	MCp
	CC (*n* = 35)	TC (*n* = 45)	TT (*n* = 6)			TT (*n* = 28)	TC (*n* = 49)	CC (*n* = 9)		
Site										
Rectum	9 (25.7%)	10 (22.2%)	0 (0%)	3.929	0.417	5 (17.9%)	12 (24.5%)	2 (22.2%)	0.952	0.960
Colon	26 (74.3%)	32 (71.1%)	6 (100%)			22 (78.6%)	35 (71.4%)	7 (77.8%)		
Rectosigmoid	0 (0%)	3 (6.7%)	0 (0%)			1 (3.6%)	2 (4.1%)	0 (0%)		
Grade										
Low	7 (20%)	10 (22.2%)	0 (0%)	2.123	0.713	7 (25%)	9 (18.4%)	1 (11.1%)	5.017	0.248
Intermediate	25 (71.4%)	29 (64.4%)	5 (83.3%)			16 (57.1%)	37 (75.5%)	6 (66.7%)		
High	3 (8.6%)	6 (13.3%)	1 (16.7%)			5 (17.9%)	3 (6.1%)	2 (22.2%)		
Dukes stage										
B	1 (2.9%)	0 (0%)	0 (0%)	3.244	0.777	1 (3.6%)	0 (0%)	0 (0%)	3.682	0.480
C	1 (2.9%)	1 (2.2%)	0 (0%)			0 (0%)	2 (4.1%)	0 (0%)		
D	33 (94.3%)	44 (97.8%)	6 (100%)			27 (96.4%)	47 (95.9%)	9 (100%)		

χ^2 chi-square test, *MC* Monte Carlo test

p: *p* value for comparing between the different categories

($p=0.26$) and multiple polyps presence ($p=0.28$), however, the corresponding patient groups were limited yielding non statistically significant results. This goes in agreement with the present study, where no significant association was detected between rs17879961 and rs1042028 polymorphisms and various clinicopathologic parameters of CRC.

Numerous lines of evidence suggest a crucial genetic role in cancer risk determination, and association studies are important in the search for susceptibility genes related to cancer [36]. In the current study, no significant association between the *SULT1A1* R213H (rs1042028) polymorphism and CRC was detected among cases and control groups.

Results of the present work suggest that *SULT1A1* R213H polymorphism shows no association with CRC development. SULT1A1 is related to activation and detoxification of various carcinogens, as well as different hormones regulation [18]. G to A transition at nucleotide 638 in *SULT1A1* gene has been shown to induce an Arg to His swap associated with reduced enzyme activity [20]. Multiple reports concluded that *SULT1A1* HH genotype was related with an increase in cancer risks, namely breast, lung and esophageal cancers37–39. These study results support the hypothesis that low *SULT1A1*H* allozyme activity reduces protection against environmental and or dietary carcinogens. However, our study did not confirm the association between *SULT1A1 and* CRC risk. Raftogianis et al. study [20] suggested that this polymorphism is related to low enzymatic activity. Enzyme activity was recorded using platelet preparations. However, the use of platelets in the determination of a specific enzymatic activity can be misleading due to methodological inability to distinguish which enzyme is responsible for the studied activity [40]. In addition, initial modelling reports showed that such polymorphism has no direct effect on the binding plot of the substrate or the universal sulphonate donor 39phosphoadenosine-59-phosphosulphate (PAPS) [41]. Supplemental future research on the functional consequences of *SULT1A1* R213H polymorphism are strongly recommended.

The results of the present study are consistent with a meta-analysis demonstrating lack of association between the *SULT1A1* R213H polymorphism and CRC, specifically in Caucasian population [42]. However, such meta-analysis results should be cautiously interpreted because *SULT1A1* R213H polymorphism prevalence may vary with various CRC subtypes; therefore, analysis classified by variable CRC subtypes may yield more accurate results.

The present study also goes in concordance with Chung Fai Won et al. [40] research on Australian population, reporting insignificant correlation between the *SULT1A1* R213H polymorphism and CRC development. Moreover, substrate assays research reported no functional difference between R213 *SULT1A1* and H213 *SULT1A1* in sulphonating the model substrate p-nitrophenol, the sulphonate donor PAPS or the drug substrate paracetamol.

Conclusion

We conclude that *CHEK2* I127T (rs17879961) and *SULT1A1* R213H (rs1042028) polymorphisms might not be associated with CRC development in Egyptian population; however, larger scale studies are recommended.

Abbreviations

Arg: Arginine; ATM: Ataxia-telangiectasia mutated; BRCA1: Breast cancer type 1 susceptibility protein; Cdc25A: Cell division cycle 25 A; Cdc25C: Cell division cycle 25 C; Cds1: CDP-diacylglycerol synthase 1; CHEK2: Checkpoint kinase 2; CRC: Colorectal cancer; FHA: Forkhead associated; His: Histidine; HWE: Hardy–Weinberg equilibrium; Ilu: Isoleucine; Mdm2: Mouse double minute 2; PCR: Polymerase chain reaction; RAD53: RADiation sensitive; RFLP: Restriction fragment length polymorphism; SCD: SQ/TQ cluster domain; *SULTs*: Sulfotransferases; Thr: Threonine.

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Authors' contributions

GME contributed to design of the work, laboratory work, interpretation of data, and drafting the work. MAE contributed to clinical data acquisition. LMD contributed to laboratory work, data analysis, and revision of the work. All authors have read and approved the manuscript.

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Availability of data and materials

Available on request.

Declarations

Ethics approval and consent to participate

The research was reviewed and approved by the Ethics Committee (IORG#: IORG0008812), Medical Research Institute, Alexandria University. Informed written consents were obtained from all participants after explanation of the purpose of the study.

Consent for publication

Informed written consent to publish was obtained from all participants who participated in the study.

Competing interests

The authors declare that they have no competing interests.

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References

1. DeSantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alcaraz KI et al (2016) Cancer statistics for African Americans, 2016: progress and opportunities in reducing racial disparities. CA Cancer J Clin 66(4):290–308
2. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M et al (2000) Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343(2):78–85
3. Torgovnick A, Schumacher B (2015) DNA repair mechanisms in cancer development and therapy. Front Genet 6:157
4. Broustas CG, Lieberman HB (2014) DNA damage response genes and the development of cancer metastasis. Radiat Res 181(2):111–130
5. Markowitz SD, Bertagnolli MM (2009) Molecular basis of colorectal cancer. N Engl J Med 361(25):2449–2460
6. Tiwari V, Wilson DM III (2019) DNA damage and associated DNA repair defects in disease and premature aging. Am J Hum Genet 105(2):237–257
7. Bernstein C, Bernstein H, Payne CM, Garewal H (2002) DNA repair/pro-apoptotic dual-role proteins in five major DNA repair pathways: fail-safe protection against carcinogenesis. Mutat Res 511(2):145–178
8. Consortium CBCC-C (2004) CHEK2* 1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am J Hum Genet 74(6):1175–1182
9. Cybulski C, Gorski B, Huzarski T, Masojć B, Mierzejewski M, Dębniak T et al (2004) CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet 75(6):1131–1135
10. de Jong MM, Nolte IM, te Meerman GJ, van der Graaf WT, Mulder MJ, van der Steege G et al (2005) Colorectal cancer and the CHEK2 1100delC mutation. Genes Chromosomes Cancer 43(4):377–382
11. Bartkova J, Hořejší Z, Koed K, Krämer A, Tort F, Zieger K et al (2005) DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 434(7035):864–870
12. Williams LH, Choong D, Johnson SA, Campbell IG (2006) Genetic and epigenetic analysis of CHEK2 in sporadic breast, colon, and ovarian cancers. Clin Cancer Res 12(23):6967–6972
13. Kilpivaara O, Vahteristo P, Falck J, Syrjäkoski K, Eerola H, Easton D et al (2004) CHEK2 variant I157T may be associated with increased breast cancer risk. IJC 111(4):543–547
14. Li J, Williams BL, Haire LF, Goldberg M, Wilker E, Durocher D et al (2002) Structural and functional versatility of the FHA domain in DNA-damage signaling by the tumor suppressor kinase Chk2. Mol Cell 9(5):1045–1054
15. Seppälä E, Ikonen T, Mononen N, Autio V, Rökman A, Matikainen M et al (2003) CHEK2 variants associate with hereditary prostate cancer. Br J Cancer 89(10):1966–1970
16. Coughtrie M (2002) Sulfation through the looking glass—recent advances in sulfotransferase research for the curious. Pharmacogen J 2(5):297–308
17. Harris R, Picton R, Singh S, Waring R (2000) Activity of phenolsulfotransferases in the human gastrointestinal tract. Life Sci 67(17):2051–2057
18. Glatt H (2000) Sulfotransferases in the bioactivation of xenobiotics. Chem Biol Interact 129(1–2):141–170
19. Dooley TP, Obermoeller RD, Leiter EH, Chapman HD, Falany CN, Deng Z et al (1993) Mapping of the phenol sulfotransferase gene (STP) to human chromosome 16p12.1–p11.2 and to mouse chromosome 7. Genomics 18(2):440–443
20. Raftogianis RB, Wood TC, Otterness DM, Van Loon JA, Weinshilboum RM (1997) Phenol sulfotransferase pharmacogenetics in humans: association of commonSULT1A1alleles with TS PST phenotype. Biochem Biophys Res Commun 239(1):298–304
21. Tumbull R, Kyle K, Watson F, Spratt J (1967) Cancer of the colon: the influence of the no-touch isolation technique on survival rates. Ann Surg 166:420–427
22. Gabriel W, Dukes C, Bussey H (1935) Lymphatic spread in cancer of the rectum. BJS 23(90):395–413
23. Miller S, Dykes D, Polesky H (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16(3):1215
24. Cybulski C, Huzarski T, Górski B, Masojć B, Mierzejewski M, Dębniak T et al (2004) A novel founder CHEK2 mutation is associated with increased prostate cancer risk. Cancer Res 64(8):2677–2679
25. Zheng W, Xie D, Cerhan JR, Sellers TA, Wen W, Folsom AR (2001) Sulfotransferase 1A1 polymorphism, endogenous estrogen exposure, well-done meat intake, and breast cancer risk. Cancer Epidemiol Biomark Prev 10(2):89–94
26. Bartek J, Lukas J (2003) Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell 3(5):421–429
27. Antoni L, Sodha N, Collins I, Garrett MD (2007) CHK2 kinase: cancer susceptibility and cancer therapy–two sides of the same coin? Nat Rev Cancer 7(12):925–936
28. Brennan P, McKay J, Moore L, Zaridze D, Mukeria A, Szeszenia-Dabrowska N et al (2007) Uncommon CHEK2 mis-sense variant and reduced risk of tobacco-related cancers: case–control study. Hum Mol Genet 16(15):1794–1801
29. Kilpivaara O, Alhopuro P, Vahteristo P, Aaltonen LA, Nevanlinna H (2006) CHEK2 I157T associates with familial and sporadic colorectal cancer. J Med Genet 43(7):e34
30. Kleibl Z, Havranek O, Novotny J, Kleiblova P, Soucek P, Pohlreich P (2008) Analysis of CHEK2 FHA domain in Czech patients with sporadic breast cancer revealed distinct rare genetic alterations. Breast Cancer Res Treat 112(1):159–164
31. Falchetti M, Lupi R, Rizzolo P, Ceccarelli K, Zanna I, Calo V et al (2008) BRCA1/BRCA2 rearrangements and CHEK2 common mutations are infrequent in Italian male breast cancer cases. Breast Cancer Res Treat 110(1):161–167
32. Bogdanova N, Enβen-Dubrowinskaja N, Feshchenko S, Lazjuk GI, Rogov YI, Dammann O et al (2005) Association of two mutations in the CHEK2 gene with breast cancer. Int J Cancer Res 116(2):263–266
33. Cybulski C, Wokołorczyk D, Kładny J, Kurzwaski G, Suchy J, Grabowska E et al (2007) Germline CHEK2 mutations and colorectal cancer risk: different effects of a missense and truncating mutations? Eur J Hum Genet 15(2):237–241
34. Kleibl Z, Havranek O, Hlavata I, Novotny J, Sevcik J, Pohlreich P et al (2009) The CHEK2 gene I157T mutation and other alterations in its proximity increase the risk of sporadic colorectal cancer in the Czech population. Eur J Cancer 45(4):618–624
35. Konstantinova D, Kadiyska T, Sokolova V, Kaneva R, Mirchev M, Savov A et al (2010) CHEK2 I157T and colorectal cancer in Bulgaria. J BUON 15(2):314–317
36. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273(5281):1516–1517
37. Xiao J, Zheng Y, Zhou Y, Zhang P, Wang J, Shen F et al (2014) Sulfotransferase SULT1A1 Arg213His polymorphism with cancer risk: a meta-analysis of 53 case-control studies. PLoS ONE 9(9):e106774
38. Forat-Yazdi M, Jafari M, Kargar S, Abolbaghaei SM, Nasiri R, Farahnak S et al (2017) Association between SULT1A1 Arg213His (Rs9282861) polymorphism and risk of breast cancer: a systematic review and meta-analysis. J Res Health Sci 17(4):e00396
39. Liang G, Miao X, Zhou Y, Tan W, Lin D (2004) A functional polymorphism in the SULT1A1 gene (G638A) is associated with risk of lung cancer in relation to tobacco smoking. Carcinogenesis 25(5):773–778
40. Wong CF, Liyou N, Leggett B, Young J, Johnson A, McManus ME (2002) Association of the SULT1A1 R213H polymorphism with colorectal cancer. Clin Exp Pharmacol Physiol 29(9):754–758
41. Bidwell LM, McManus ME, Gaedigk A, Kakuta Y, Negishi M, Pedersen L et al (1999) Crystal structure of human catecholamine sulfotransferase. J Mol Biol 293(3):521–530
42. Zhang C, Li J-P, Lv G-Q, Yu X-M, Gu Y-L, Zhou P (2011) Lack of association of SULT1A1 R213H polymorphism with colorectal cancer: a meta-analysis. PLoS ONE 6(6):e19127

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