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Genetic polymorphism of glutathione S-transferase T1 and the risk of colorectal cancer: A meta-analysis

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ABSTRACT

Background: Studies investigating the association between genetic polymorphism of glutathione S-transferase T1 (GSTT1) and risk of colorectal cancer have reported conflicting results. In order to clarify the effect of GSTT1 polymorphism on the risk of developing colorectal cancer, we carried out a meta-analysis using published data to obtain more precise estimates of risk. *Methods*: Electronic searches of PubMed and EMBASE were conducted to select studies for this meta-analysis. Papers were included if they were observational studies investigating the association between GSTT1 polymorphism and colorectal cancer risk. The principal outcome measure was the odds ratio (OR) with 95% confidence interval (CI) for the risk of colorectal cancer associated with GSTT1 null genotype. *Results*: We identified 30 eligible studies, which included 7635 cases and 12,911 controls. The combined results based on all studies showed that there was a statistically significant link between GSTT1 null genotype and colorectal cancer risk (OR = 1.20, 95% CI = 1.03–1.40). In the analysis of ethnic groups, we observed distinct differences associated with GSTT1 null genotype, the pooled odds ratios for the GSTT1 polymorphism were 1.32 in Caucasians (95% CI = 1.09–1.58) and 1.03 in Asians (95% CI = 0.81–1.32). As far as concerned the interaction between GSTT1 genotype and colorectal cancer risk in relation to smoking history, there was no increase in risk for smokers or nonsmokers with the GSTT1 null genotype (smokers: OR = 1.13, 95% CI = 0.80–1.60, nonsmokers: OR = 0.99, 95% CI = 0.71–1.38). When stratifying by the location of colorectal cancer, we found that there was a statistically significant link in rectal cancer (OR = 1.50, 95% CI = 1.09–2.07), but not in colon cancer (OR = 1.33, 95% CI = 0.94–1.88). No associations could be detected between null GSTT1 polymorphism and age, sex, tumor stage and differentiation. *Conclusion*: Our current study demonstrates that GSTT1 null genotype is associated with an increased risk of colorectal cancer, specifically, among Caucasians.

1. Introduction

With about 1 million new cases worldwide in 2002 (9.4% of the total of all cancers), colorectal cancer is one of the most frequent malignant tumors and a leading cause of cancer-related death. In terms of incidence, colorectal cancer ranks fourth in frequency in men and third in women [1]. It is most frequent in North America, Western Europe, Australia/New-Zealand and the southern part of South America [2]. Some of the more developed and westernized Asian countries have already experienced a rapidly rising trend at present, and the incidence is similar to the west [3].

The increasing incidence rates may be due to some environmental factors, which can lead to the carcinogenesis of colorectal cancer. Some epidemiological studies have revealed that diets high in red meat, low in vegetables and fiber, obesity, and smoking are probably important etiological factors increasing the risk of developing colorectal cancer [4–7]. However, colorectal cancer development requires a complex interaction between genetic and specific environmental/life style risk factors with different degrees of involvement [8]. Its onset is likely to involve multiple genes with moderate effects and progress materializes due to aggressive gene–environment interactions [9,10].

Among various candidate genes implicated in colorectal cancers, are the glutathione S-transferases (GSTs). GSTs are a multigene family of dimeric enzymes that inactivate carcinogens by catalyzing the conjugation of electrophiles to glutathione [11]. They are divided into two microsomal and numerous cytosolic GST-classes (alpha, mu, kappa, pi, sigma, theta and zeta) [12]. GSTs are involved in the metabolism of many xenobiotics, including an array of environmental carcinogens, chemotherapeutic agents and endogenously derived reactive oxygen species [11]. The theta class gene, GSTT1, is located on chromosome 22q 11.2 [13]. It has a functional and a non-functional allele. Homozygosity for the non-functional allele of GSTT1 (null genotype) causes an absence of

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GSTT1 enzyme activity [14]. Individuals with GSTT1 null genotype may have an impaired ability to metabolically eliminate carcinogens and may therefore be at increased cancer risk, including colorectal cancer.

Over the last two decades, a number of studies on the association between the GSTT1 polymorphism and colorectal cancer have been published. Some studies have shown the GSTT1 polymorphism to be associated with increased susceptibility to colorectal cancer. However, other studies have failed to replicate such an association. In order to clarify the effect of GSTT1 polymorphism on the risk of developing colorectal cancer, we carried out a meta-analysis using published data from 1990 to May 2009 to obtain more precise estimates of risk.

2. Materials and methods

2.1. Identification of relevant studies

We searched the following electronic databases: PubMed and EMBASE, using the combined key words: 'GSTT1', 'Glutathione S-transferase T1', 'polymorphism', 'genetics', 'colorectal cancer', 'colon cancer', 'rectal cancer', published from 1990 to May 2009. The citations in identified articles and in review articles were also examined. We did not consider abstracts or unpublished reports.

2.2. Inclusion and exclusion criteria

The criteria for acceptance of the studies were as follows: (1) independent case–control or cohort studies for human; (2) each study should have the similar research goal with the identical study method; (3) the main factors of these studies should be related to GSTT1 polymorphism and risk of colorectal cancer. And for the exclusion criteria, we provided as follows: (1) studies without raw data we need; (2) studies that focused on hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP) or colorectal adenoma; (3) duplicated studies.

2.3. Data extraction

Data were extracted and entered into a database. The extraction was done by two researchers independently, according to the pre-specified selection criteria. Any disagreement was resolved by discussion. The following information was sought from each study: investigators; year of publication; country of study; ethnic origin; study design (categorized as hospital-based case–control studies, population-based case–control studies); the number of cases and controls with GSTT1 null and positive genotype; variables investigated in the studies (age, sex, smoking history, tumor location, stage and differentiation).

2.4. Statistical analysis

The statistical analysis was performed by use of RevMan5.0, which was provided by Cochrane Collaboration. $P < 0.05$ was considered statistically significant. Meta-analysis was done with either the random-effects model or fixed effects model. Heterogeneity was checked by the χ^2-test. In addition, we used I^2 statistic to quantify the effect of heterogeneity, providing a measure of the degree of inconsistency in the studies' results. If the results of the trials had heterogeneity, the random-effects model was used. To establish the effect of clinical heterogeneity between studies on meta-analysis conclusions, subgroup analyses were conducted on the basis of sex; age; ethnic origin; smoking history; tumor location, stage and differentiation. The results were expressed with odds ratio (OR) for the categorical variables and 95% confidence interval (CI).

Table 1
Summary of case–control studies of GSTT1 polymorphism and colorectal cancer risk.

Investigators	Year	Study design	Country	Ethnic origin	GSTT1 null		GSTT1positive	
					Cases	Controls	Cases	Controls
Chenevix-Trench et al. [23]	1995	HCC	Australia	Caucasians	17	23	108	125
Deakin et al. [24]	1996	HCC	Canada	Caucasians	63	94	148	415
Katoh et al. [25]	1996	HCC	Japan	Asians	50	56	53	70
Gertig et al. [26]	1998	PCC	USA	Caucasians	36	51	173	169
Abdel-Rahmana et al. [27]	1999	HCC	Egypt	Caucasians	22	21	37	30
Welfare et al. [28]	1999	PCC	UK	Caucasians	35	30	142	147
Zhang et al. [29]	1999	PCC	Sweden	Caucasians	50	22	44	87
Butler et al. [30]	2001	PCC	Australia	Caucasians	67	40	123	160
Loktionov et al. [31]	2001	HCC	UK	Caucasians	40	54	166	301
Saadat and Saadat [32]	2001	PCC	Iran	Caucasians	18	41	28	90
Laso et al. [33]	2002	HCC	Spain	Caucasians	43	33	204	263
Sachse et al. [34]	2002	PCC	UK	Caucasians	184	215	306	378
Seow et al. [35]	2002	PCC	Singapore	Asians	80	480	133	710
Ye and Parry [36]	2002	HCC	UK	Caucasians	2	9	39	73
Zhu et al. [37]	2002	HCC	China	Asians	63	48	41	53
Nascimento et al. [38]	2003	HCC	Brazil	Mixed[a]	17	52	85	248
van der Hel et al. [39]	2003	PCC	Netherlands	Caucasians	58	224	154	541
Chen et al. [40]	2004	PCC	China	Asians	23	69	102	270
Kiss et al. [41]	2004	HCC	Hungary	Caucasians	131	108	369	392
van der Logt et al. [42]	2004	PCC	Netherlands	Caucasians	72	69	299	346
Ates et al. [43]	2005	PCC	Turkey	Caucasians	63	53	118	151
Rajagopal et al. [44]	2005	HCC	UK	Caucasians	96	158	265	723
Yeh et al. [45]	2005	HCC	China	Asians	396	360	327	373
Huang et al. [46]	2006	PCC	USA	Whites/blacks	130	271	428	603
Little et al. [47]	2006	PCC	Scotland	Caucasians	49	65	192	318
Martinez et al. [48]	2006	PCC	Spain	Caucasians	74	76	68	253
Probst-Hensch et al. [49]	2006	PCC	Singapore	Asians	100	475	200	693
Skjelbred et al. [50]	2007	HCC	Norway	Caucasians	15	37	93	262
Küry et al. [51]	2008	PCC	France	Caucasians	183	205	840	916
Epplein et al. [52]	2009	PCC	USA	Mixed[b]	46	112	127	201

HCC: hospital-based case–control; PCC: population-based case–control
[a] Whites and blacks.
[b] African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites.