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Review Article

The Association of Genetic Polymorphisms on the Risk of Developing of Colorectal and Bladder Carcinomas

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Abstract

Within this review a brief overview is presented of the current knowledge of the genetic polymorphisms of the N-acetyltransferase and glutathione-S-transferase enzymes, the apoptotic inhibitor enzyme surviving and the bio transformer UDP-glucuronosyltransferase, focusing on the association of such polymorphisms on the risk of developing of colorectal and bladder carcinomas. Studies identifying the effects of nullification of various genes to the risk of developing colorectal and bladder cancer are described. It was determined that understanding polymorphism involved in colorectal and bladder cancer can not only create potential pharmaceutical treatment targets, but also can identify possible biomarkers.

Keywords: Genetic Polymorphisms; Colorectal; Bladder Carcinomas

Abbreviations

GSTM1: Glutathione S-Transferase M1; GSTT1: Glutathione S-Transferase T1; PAH: Polycyclic Aromatic Hydrocarbons; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; UGT: UDP-Glucuronosyltransferases

Introduction

Bladder cancer is the fourth or fifth most common cancer in Europe and the United States [1,2], with over 90% of bladder cancers being of transitional cell types [3]. Approximately 60% of all cases occur in men, with the average age of diagnosis being 65 years of age [4]. Identified risk factors include smoking, aniline dye exposure, and previous radiotherapy; in countries where it is endemic, schistosomiasis is also an important cause of squamous cell bladder cancer [5].

Most large bowel cancers arise within pre-existing intestinal polyps, half of which occur in the rectum and around 20% in the sigmoid colon. Direct invasion of neighbouring structures may occur with metastatic spread to the lymph nodes, lungs, bone, and in particular, liver. More than half of patients diagnosed with bowel cancer will develop metastases, and up to a quarter present with metastatic disease. Signs and symptoms are non-specific and include rectal bleeding, anaemia, abdominal pain, altered bowel habit and weight loss. Depending where the tumour is located, there may be local obstruction or perforation. Screening is effective in reducing mortality, although the ideal method to be used is controversial [5].

Several studies investigating single-nucleotide polymorphisms in relation to bladder carcinoma have identified various associated genetic polymorphisms of detoxification or DNA repair genes, such as the N-acetyl transferase and glutathione S-transferase genes [6-10].

Colorectal cancer is the third most common cancer and the fourth most common cause of death from cancer worldwide, accounting for an estimated 1,330,000 new cases and 608,000 cancer deaths in 2008 [4].

In developed countries such as Europe and the USA, colorectal cancers are very common [11]; however colorectal cancer is rare among African and Asian populations [12]. As with most carcinomas the mechanisms underlying the development of colorectal cancer are complex, but it is understood that colorectal adenomatous polyps are precursors of colorectal cancer [13,14]. Genetic, environmental, lifestyle (such as smoking), and dietary

factors are thought to contribute to development of colorectal cancer, which supports the association with polymorphisms as they affect environmental and dietary factor metabolism. Inherited predisposition syndromes include hereditary non-polyposis colorectal cancer and familial adenomatous polyposis, and genetic epidemiology and twin studies demonstrate that more than 35% of colorectal cancer cases may be due to inherited genetic polymorphisms [15].

Genetic polymorphisms are categorised based on their primary cellular functions: genes in carcinogen metabolism, apoptosis, cell cycle control, DNA repair, inflammation, methylation, genes functioning as G proteins, and cell adhesion molecules. The possible array of mutations in these genes gives rise to the complexity in the pathogenesis of cancers such as bladder and co-rectal. Due to the allowed length of this mini-review, the full array of polymorphisms cannot be discussed and as such the mini-review will focus on well-studied polymorphisms.

Polymorphisms affecting the metabolism of carcinogens

N-acetyl transferase and glutathione S-transferase isoenzymes are two widely studied polymorphisms that affect the metabolism of carcinogens [16,17].

N-acetyltransferase 1 (*NAT1*) and 2 (*NAT2*) are the products of single, intron less, protein coding exons the genes of which are located on human chromosome 8p22 [18]. The coding regions of *NAT1* and *NAT2* share 87% nucleotide homology, yielding 55 amino acid differences [19]. The two NAT isoenzymes are polymorphic and catalyse both the O-acetylation (normally activation) and the N-acetylation (normally deactivation) of aromatic and heterocyclic amine carcinogens. The NATs were among the first drug-metabolising enzymes shown to demonstrate genetic variation in humans [20] and the two different NAT isoenzymes have different catalytic activities affecting their metabolism of carcinogens.

NAT2 is an important enzyme in detoxifying carcinogens, especially within bladder cells. Slow and rapid acetylators have been shown to have variable association with bladder cancer [21,22] and the slow *NAT2* acetylator phenotype is associated with a decreased risk of colorectal cancer [22,23]. *NAT2* slow acetylators have been shown in early pooled studies, to moderately increase the risk of bladder cancer, when compared with rapid acetylators [24]. A case-control study in Japan demonstrated that the *NAT2* slow genotype was significantly associated with an increased bladder cancer risk (OR = 3.41, 95% CI = 1.68-6.87), and this risk was further enhanced with tobacco smoking (8.57, 1.82 - 40.25) [25].

The glutathione S-transferase M1 (*GSTM1*) and glutathione S-transferase T1 (*GSTT1*) genes code for cytosolic enzymes involved in phase II metabolism; glutathione S-transferase (GST)-u and GST-8, respectively. Deletions of either genes have been identified. The GST family of enzymes play a key role in the detoxification of exogenous substrates such as; xenobiotics, carcinogenic compounds and environmental substances [26,27]. Eight distinct gene families encode these soluble GSTs in humans; alpha, chi (also known as omega), kappa, mu, pi, theta, sigma and zeta [27]. There are several polymorphic GSTs.

The group mu originating enzyme *GSTM1* detoxifies carcinogenic polycyclic aromatic hydrocarbons (PAH) and a null *GSTM1* genotype is associated with increased susceptibility to bladder cancer due to reduced PAH detoxification [27-29]. Colorectal cancer has been inconsistently associated with PAH exposure from diet and tobacco [29].

The association of the relative risk of various cancers with polymorphisms of *GSTM1, GSTT1*, and *GSTP1* genes has been widely assessed, with the most thoroughly studied being the *GSTM1* and *GSTT1* null polymorphisms, and *GSTP1* 313 adenosine to glutamine substitutions. *GSTP1* substitution of isoleucine with valine at codon 105 polymorphisms are thought be a risk factors for bladder cancer and does not show any significant difference between smokers and non-smokers [30].

Carcinogenic PAHs, such as the tobacco carcinogen benzopyrene are detoxified by *GSTM1* while smaller reactive hydrocarbons, such as ethylene oxide are detoxified by *GSTT1* [31]. A wide range of xenobiotics are conjugated and detoxified by *GSTP1* [32]. Null genotypes of *GSTM1* and *GSTT1* lead to the loss of this enzymatic activity. *GSTM1* is understood to detoxify the carcinogenic PAHs and a null genotype is associated with increased susceptibility to bladder cancer [33]. The deletion of one or two copies of the *GSTM1* gene has been shown in a Spanish study to increase the risk of developing bladder cancer by 1.2-fold or 1.9-fold, respectively. Meta-analysis studies also confirm that the *GSTM1* deletion genotype contributes to bladder cancer risk, even after adjustments are made for smokers [34]. Consistency of results has been found in the association between *GSTT1* genotype and bladder cancer risk in various studies [8].

Two distinct forms of the *GSTP1* are known, which arise by the single base pair substitution of adenosine to glutamine at nucleotide 313 of the *GSTP1* gene. Individuals with the null genotype for *GSTT1* have been shown to have an increased risk of developing bladder cancer [6,35]. Nucleotide level polymorphism of *GSTP1*

313 adenosine to glutamine leads to a variation of isoleucine to valine at codon 105 and this valine amino acid substitution results in reduced enzymatic activity [28].

As GST enzymes are involved in the metabolism of PAHs, null genotypes would be expected to modify the risk of developing colorectal cancer risk due to increased PAH exposure. From analysing case control studies, evidence suggests that *GSTM1* is involved in the etiology of colorectal cancers [36], although not all studies have shown this and the inconsistency in results of the association between *GSTM1* or *GSTT1* genotype and colorectal cancer are well documented.

Most studies have methodological limitations and few studies have investigated environmental factors on genetics. A polyp study suggested an interaction between *GSTM1* genotype and smoking [37]. GST nonnull genotype has been suggested to increased disease risk in subjects with high red meat intake [29]. *GSTM1* null patients are likely to benefit greatly from broccoli consumption as a strong inverse relation between colorectal adenomas and broccoli consumption is known [29]. Such findings require confirmation and consistency.

Survivin polymorphisms

Survivin is a member of the inhibitor apoptosis protein family and is involved in the regulation of cell division, it has been shown to prevent programmed cell death via both extrinsic and intrinsic pathways thorough inhibiting the two early apoptotic enzymes caspase-3 and caspase-7 [38]. Down-regulation of survivin by the naturally occurring flavanone, silibinin has been associated with a strong and prominent caspases-9 and -3 activation; identifying survivin's potential as a pharmaceutical target. Survivin polymorphisms have been shown to have links to genetic susceptibility to various tumours, including but not limited to, bladder and colorectal carcinomas, however the results are inconsistent and inconclusive [39-41]. The link between survivn with increased bladder and colorectal cancer development is supported by the high expression of survivn in such tumours and the inability to trace the protein in adjacent normal tissues, either immunohistochemical staining or by PCR analysis [42]. This high expression also identifies why Survivin is considered to be a potential carcinoma biomarker [43].

In the Asian population, the survivin rs9904341 is thought to contribute to an increased susceptibility to various cancers including colorectal and bladder cancers [39,44]. Conversely the survivin rs17878467 T allele might be a protective factor for such tumours, in particular the Asian population [41,45]. Survivins rs8073069 and rs2071214 seem to be associated with an increased tumour risk in Asians, while there was no association between the survivin rs1042489 and tumour risk [41,45].

UDP-glucuronosyltransferases polymorphisms

The phase II metabolism of exogenous and endogenous compounds is facilitated by UDP-glucuronosyltransferases (UGT). A possible etiology of colorectal cancer is thought to involve the glucuronidation of dietary factors by UGT, thus polymorphisms of such an enzyme would affect colorectal cancer risk through altering levels of exposure of dietary factors.

Analysis of *UGT1A* demonstrates that the C-T-G haplotype in the 3′ region flanking the *UGT1A* shared exons increases male colorectal cancer risk (OR = 2.56, 95% CI = 1.10 - 5.95) and the A-G-T haplotype in the *UGT1A* shared exons decreases colorectal cancer risk [7]. UGT polymorphisms alter colorectal cancer risk differently by anatomical sub-site and gender [7].

Non-steroidal anti-inflammatory drugs (NSAIDs) use is associated with a reduction in the risk of developing colorectal carcinoma [46], this protective factor is understood to rely on NSAID's metabolism by UGT [46]. Polymorphisms in the *UGT1A* shared exons can have a regulatory effect on gene expression increasing a protective effect of NSAIDs on colorectal cancer risk [7].

Conclusion

The etiology of bladder and co-rectal carcinomas is complex, with there being various genetic polymorphisms, environmental and dietary factors all coming into play affecting the risk and development of both diseases. The role of the polymorphisms in bladder and co-rectal cancer risk is without doubt, especially. The polymorphisms such as survivin do allow the opportunity to develop pharmaceuticals to target a gene or protein to treat bladder and co-rectal carcinomas. Designing medicines to block or reduce polymorphisms that increase risk is a viable option for pharmaceutical companies as is designing medicines to enhance polymorphism that reduce the risk of developing bladder and co-rectal carcinomas, such as a *UGT1A* enhancer.

Polymorphisms can also be used a biomarker, in particular survivin which is highly expressed in tumours but absent in normal tissue indicating that it could be an interesting diagnostic marker that may be independent of cut-off levels.

Smoking plays a large part in cancer development especially particular polymorphisms, which is understandable as various alleles will affect the metabolism of the carcinogenic compounds of smoking and increased exposure of tissues.

More studies are required to explain if some polymorphisms can serve as predictive and prognostic factors in bladder and co-rectal carcinogenesis. Studies without methodological limitations are also needed, to clearly identify the associations of environment, lifestyle including smoking with the various polymorphisms to developing carcinomas. As with some there is evidence of an increased combined risk and others there is none.

Bibliography

1. Boustead GB., *et al*. "Stage, grade and pathological characteristics of bladder cancer in the UK: British Association of Urological Surgeons (BAUS) Urological Tumour Registry". *BJU International* (2013).

2. Kaplan AL., *et al*. "The future of bladder cancer care in the USA". *Nature Review Urology* 11 (2014): 59-62.

3. Kontos S., *et al*. "Inverse expression of estrogen receptor-beta and nuclear factor-kappaB in urinary bladder carcinogenesis". *International Journal of Urology* 17 (2010): 801-809.

4. Jemal A., *et al*. "Cancer statistics, 2008". *CA Cancer Journal of Clinician* 58 (2008): 71-96.

5. Sweetman SC and Martindale W. "Martindale: the complete drug reference, (Pharmaceutical Press, London, 2011)".

6. Abdel-Rahman SZ., *et al*. "GSTM1 and GSTT1 genes are potential risk modifiers for bladder cancer". *Cancer Detection and Prevention* 22 (1998): 129-138.

7. Angstadt AY., *et al*. "The effect of UGT1A and UGT2B polymorphisms on colorectal cancer risk: haplotype associations and gene-environment interactions". *Genes Chromosomes Cancer* 53 (2014): 454-466.

8. Garcia-Closas M., *et al*. "NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses". *Lancet* 366 (2005): 649-659.

9. Gertig DM., *et al*. "Glutathione S-transferase GSTM1 and GSTT1 polymorphisms and colorectal cancer risk: a prospective study". *Cancer Epidemiology, Biomarkers and Prevention* 7 (1998): 1001-1005.

10. Jourenkova-Mironova N., *et al*. "Role of glutathione S-transferase GSTM1, GSTM3, GSTP1 and GSTT1 genotypes in modulating susceptibility to smoking-related lung cancer". *Pharmacogenetics* 8 (1998): 495-502.

11. Allemani C., *et al*. "Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study". *BMJ Open* 3 (2013): e0030553.

12. Shin HR. "[Global activity of cancer registries and cancer control and cancer incidence statistics in Korea]". *Journal of Preventive Medicine and Public Health* 41 (2008): 84-91.

13. Siamakpour-Reihani S., *et al*. "Systemic markers of oxidative status and colorectal adenomatous polyps". *Annals of Epidemiology* 22 (2012): 587-591.

14. Imperiale TF and Ransohoff DF. "Risk for colorectal cancer in persons with a family history of adenomatous polyps: a systematic review". *Annals of Internal Medicine* 156 (2012): 703-709.

15. Markowitz SD and Bertagnolli MM. "Molecular origins of cancer: Molecular basis of colorectal cancer". *The New England Journal of Medicine* 361 (2009): 2449-2460.

16. Ratliff TL. "Effects of N-acetyl transferase 1 and 2 polymorphisms on bladder cancer risk in Caucasians". *Journal of Urology* 174 (2005): 2066.

17. Vineis P., *et al*. "Genetic susceptibility according to three metabolic pathways in cancers of the lung and bladder and in myeloid leukemias in nonsmokers". *Annals of Oncology* 18 (2007): 1230-1242.

18. Franekova M., *et al*. "Gene polymorphisms in bladder cancer". *Urologic Oncology* 26 (2008): 1-8.

19. Volanis D., *et al*. "Molecular mechanisms in urinary bladder carcinogenesis". *JBUON* 16 (2011): 589-601.

20. Weber WW and Hein DW. "N-acetylation pharmacogenetics". *Pharmacological Reviews* 37 (1985): 25-79.

21. Green J., *et al*. "N-acetyltransferase 2 and bladder cancer: an overview and consideration of the evidence for gene-environment interaction". *British Journal of Cancer* 83 (2000): 412-417.

22. Vineis P., *et al*. "Current smoking, occupation, N-acetyltransferase-2 and bladder cancer: a pooled analysis of genotype-based studies". *Cancer Epidemiology, Biomarkers and Prevention* 10 (2001): 1249-1252.

23. Marcus PM., *et al*. "NAT2 slow acetylation and bladder cancer risk: a meta-analysis of 22 case-control studies conducted in the general population". *Pharmacogenetics* 10 (2000): 115-122.

24. Carreon T., *et al*. "NAT2 slow acetylation and bladder cancer in workers exposed to benzidine". *International Journal of Cancer* 118 (2006): 161-168.

25. Ward E., *et al*. "Association of insurance with cancer care utilization and outcomes". *CA Cancer Journal of Clinician* 58 (2008): 9-31.

26. Schnakenberg E., *et al*. "Susceptibility genes: GSTM1 and GSTM3 as genetic risk factors in bladder cancer". *Cytogenetic and Genome Research* 91 (2000): 234-238.

27. Strange RC., *et al*. "Glutathione-S-transferase family of enzymes". *Mutation Research* 482 (2001): 21-26.

28. Srivastava DS., *et al*. "Genetic polymorphism of glutathione S-transferase genes (GSTM1, GSTT1 and GSTP1) and susceptibility to prostate cancer in Northern India". *BJU International* 95 (2005): 170-173.

29. Cotton SC., *et al*. "Glutathione S-transferase polymorphisms and colorectal cancer: A HuGE review". *American Journal of Epidemiology* 151 (2000): 7-32.

30. Kellen E., *et al*. "Pooled analysis and meta-analysis of the glutathione S-transferase P1 Ile 105Val polymorphism and bladder cancer: A HuGE-GSEC review". *American Journal of Epidemiology* 165 (2007): 1221-1230.

31. Lee KM., *et al*. "N-acetyltransferase (NAT1, NAT2) and glutathione S-transferase (GSTM1, GSTT1) polymorphisms in breast cancer". *Cancer Letter* 196 (2003): 179-186.

32. Ye Z and Song H. "Glutathione s-transferase polymorphisms (GSTM1, GSTP1 and GSTT1) and the risk of acute leukaemia: a systematic review and meta-analysis". *European Journal of Cancer* 41 (2005): 980-989.

33. Wan H., *et al*. "Genetic polymorphism of glutathione S-transferase T1 and the risk of colorectal cancer: a meta-analysis". *Cancer Epidemiology* 34 (2010): 66-72.

34. Cui X., *et al*. "Association of genotypes of carcinogen-metabolizing enzymes and smoking status with bladder cancer in a Japanese population". *Environmental Health and Preventive Medicine* 18 (2013): 136-142.

35. Srivastava DS., *et al*. "Polymorphism of GSTM1 and GSTT1 genes in bladder cancer: a study from North India". *Archives of Toxicology* 78 (2004): 430-434.

36. Rebbeck TR. "Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility". *Cancer Epidemiology Biomarkers Prevention* 6 (1997): 733-743.

37. Matthias C., *et al*. "Polymorphism in cytochrome P450 CYP2D6, CYP1A1, CYP2E1 and glutathione S-transferase, GSTM1, GSTM3, GSTT1 and susceptibility to tobacco-related cancers: studies in upper aerodigestive tract cancers". *Pharmacogenetics* 8 (1998): 91-100.

38. Arbab IA., *et al*. "Dentatin Induces Apoptosis in Prostate Cancer Cells via Bcl-2, Bcl-xL, Survivin Downregulation, Caspase-9, -3/7 Activation, and NF-kappaB Inhibition". *Evidence-Based Complementary and Alternative Medicine* (2012): 856029.

39. Jang JS., *et al*. "Polymorphisms in the survivin gene and the risk of lung cancer". *Lung Cancer* 60 (2008): 31-39.

40. Borbely AA., *et al*. "Survivin promoter polymorphism and cervical carcinogenesis". *Journal of Clinical Pathology* 60 (2007): 303-306.

41. Kawata N., *et al*. "Two survivin polymorphisms are cooperatively associated with bladder cancer susceptibility". *International Journal of Cancer* 129 (2011): 1872-1880.

42. Fukuda S and Pelus LM. "Survivin, a cancer target with an emerging role in normal adult tissues". *Molecular Cancer Therapeutics* 5 (2006): 1087-1098.

43. Ku JH., *et al*. "Urine survivin as a diagnostic biomarker for bladder cancer: a systematic review". *BJU International* 110 (2012): 630-636.

44. Chu XY., *et al*. "Overexpression of survivin is correlated with increased invasion and metastasis of colorectal cancer". *Journal of Surgical Oncology* 105 (2012): 520-528.

45. Zhu Y., *et al*. "Association of survivin polymorphisms with tumor susceptibility: a meta-analysis". *PLoS One* 8 (2013): e74778.

46. Scherer D., *et al*. "Genetic variation in UGT genes modify the associations of NSAIDs with risk of colorectal cancer: Colon cancer family registry". *Genes Chromosomes Cancer* 53 (2014): 568-578.

Volume 2 Issue 10 October 2018