Can Alpha-1 Antitrypsin be Involved in the Carcinogenesis of Colorectal Cancer?

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Received Date: July 13, 2016, Accepted Date: August 24, 2016, Published Date: September 05, 2016.

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Abstract

Objective: To identify and assess the evidence for an association between colorectal carcinoma (CRC) and alpha-1 antitrypsin (AAT) deficiency (AATD) through a review of the existing literature.

Review Methods: The two authors of the present review independently searched for English language articles enlisted in the MEDLINE®, PubMed®, Embase, and Google Scholar databases. The Oxford Centre for Evidence-Based Medicine (CEBM) guidelines were applied to assess the quality of evidence for each study. The highest level of evidence was scored as sufficient (level 3a or higher of the Oxford CEBM Levels of Evidence 2009) or insufficient.

Results: Five studies, representing 2625 patients with CRC and 2959 general population controls were included for analysis. Levels of evidence varied from CEBM level 3a (n = 1) to 3b (n = 3) and 4 (n = 1).

Conclusion: The literature shows some controversial evidence about a hypothetical coexistence between AATD and CRC, but the evidence for a causal association is limited. Based on current data, this hypothesis cannot be demonstrated and more studies are needed to answer this question.

Keywords: Alpha-1 Antitrypsin; Alpha-1 Antitrypsin Deficiency; Colorectal Cancer; Carcinogenesis

Abbreviations

AAT: Alpha-1 Antitrypsin; AATD: Alpha-1 Antitrypsin Deficiency; CEBM: Centre for Evidence-Based Medicine; COPD: Chronic Obstructive Pulmonary Disease; CRC: Colorectal Carcinoma or Colorectal Cancer; MMR: Mismatch Repair; MSI: Microsatellite Instability; MSI-H: High Microsatellite Instability; MSI-L: Low Microsatellite Instability; MSS: Microsatellite Stable; NSAID: Non-Steroidal Anti-Inflammatory Drugs; Pi*: Protease Inhibitor

Introduction

Alpha-1 antitrypsin (AAT) is a serine protease inhibitor with anti-inflammatory, anti-apoptotic, and immunomodulatory properties [1]. The AAT gene has two alleles, which are transmitted from the parents to their children by autosomal co-dominant Mendelian inheritance. Normal alleles, present in 85–90% of individuals, are designated M, and therefore, a normal individual shows an MM genotype. The most prevalent deficiency alleles are designated S and Z, and their prevalence in Caucasian populations ranges from 5 to 10% and 1 to 3%, respectively. Consequently, the vast majority of genotypes result from combinations of M, S and Z, that is: MM (normal genotype present in about 85–95% people, expressing 100% of AAT), MS, SS, MZ, SZ, and ZZ (five deficiency genotypes present in 5–15% of remaining people, expressing grosso modo 80, 60, 55, 40, and 15% of AAT, respectively [1,2] (Table 1).

Alpha-1 antitrypsin deficiency (AATD) is a hereditary condition that predisposes to premature onset of chronic obstructive pulmonary disease (COPD) especially in smokers, liver cirrhosis, neutrophilic panniculitis, systemic vasculitis, and possibly other inflammatory diseases [3,4].

Although AAT has been recognized as a potential tumor marker, its role in cancer biology remains unknown. Nevertheless, several clinical studies have shown that subjects with AATD have an increased risk of developing hepatocellular carcinomas [5,6], and although not fully proved, it has been reported that AATD can favor the development of other malignances such as: lung cancer [6-11], neoplasms of the urinary bladder [12], gallbladder [13], malignant lymphomas [14], and colon carcinomas [15-17].

Colorectal carcinoma (CRC) is mostly related to older age, male gender, high intake of fat, alcohol or red meat, obesity, smoking and lack of physical activity, and only a small number of cases are due to inflammatory bowel disease or underlying genetic disorders, including familial adenomatous polyposis and hereditary non-polyposis colon cancer [18]. Since the relationship between AATD and CRC is a hypothetic subject currently, the objective of the present review is to analyze this subject through an evidence-based analysis of the existing literature.

Methods

To identify potentially relevant articles about the topic, the two authors independently performed a literature search of articles published between 1965 and 2016 in MEDLINE®, PubMed®, Embase, and Google Scholar databases. The following search terms were used: "Alpha-1 antitrypsin", "Alpha-1 antitrypsin deficiency", "Colorectal cancer" and "Carcinogenesis". Combining these search terms, a total of 83 articles were obtained. Titles and abstracts were assessed, and when they were not sufficiently explicit, the full text of the papers was analyzed. Many repeated articles and those with redundant content were eliminated. Additional publications with potentially interesting content cited in the bibliographies of the retrieved articles were also collected. Only population-based case-control (clinic-based) studies were retrieved for analysis. Inclusion criteria were: (1) Patients with CRC pathologically diagnosed by biopsy; (2) AAT testing assessed by: (a) AAT serum concentrations measured by nephelometry, (b) Phenotype analysis performed by isoelectric focusing, or (c) genotype assay with PCR and subsequent melting curve analysis to identify the S and Z deficiency alleles (All these criteria must be completed; the absence of either of these criteria was exclusionary). Discrepancies in selection were always resolved by discussion and re-review. Evidence-based recommendations of The Oxford Centre for Evidence-Based Medicine (CEBM) guidelines were applied to assess the study quality of evidence and to grade the retrieved articles (Table 2). The highest level of evidence was scored as sufficient (level 3a or higher of the Oxford CEBM Levels of Evidence 2009) or insufficient [19].
Citation: Holanda SP, Blanco I (2016) Can Alpha-1 Antitrypsin be Involved in the Carcinogenesis of Colorectal Cancer?. J Gastro Hepato Dis 2(1): 109.

Results

Finally, with the above criteria, five articles were selected for analysis [15-18,20,21]. The results of these selected studies are shown in table 3. The designs, results and conclusions of the five selected studies are briefly summarized as follows:

Study 1

Based on this: (1) microsatellite instability (MSI) is a genomic alteration observed in 15-30% of colorectal cancer (CRC); (2) two MSI phenotypes have been defined for CRC: High MSI (MSI-H) characterized by MSI at ≥ 30% of the examined loci, and low MSI (MSI-L) by MSI at 1-30% of the loci; (3) an absence of MSI at any loci is defined as microsatellite stable (MSS) phenotype; and (5) the majority of MSI tumors are the result of defective DNA mismatch repair (MMR), a clinic-based study was conducted at the Mayo Clinic Foundation (Rochester, Minnesota, USA) in 2000. The objective of this study was to determine the AATD "carrier status" (or Protein Inhibitor, Pi*, AAT heterozygosity, a term which mainly includes heterozygote phenotypes MS and MZ) of 161 CRC patients whose MSI phenotype and protein expression states were previously determined. Among 51 CRC patients with MSI-H tumors, the AAT-carrier MS and MZ rate was 21.6%; among 110 patients with MSI-L/MSS tumors, the rate was 9.1% (MSI-H vs MSI-L/MSS, \( P = 0.02 \)); and among the 191 population-based controls the AAT-carrier rate was 9.4% (MSI-H vs controls, \( P = 0.02 \)). The estimated relative risk of having MSI-H CRC among AATD heterozygotes was 3.1 after adjusting for age, gender, and smoking history. The risk of having MSI-H CRC among current and past smokers was 6.6 and 2.7, respectively. Patients who were AATD-carriers and smoked had a 20-fold increased risk of developing an MSI-H CRC compared to nonsmokers who were normal AAT homozygotes (i.e.: MM). These findings suggested an etiologic link between AAT alleles, inhalation of toxic fumes, and/or different favoring genes not well identified so far. It is necessary the presence of other environmental or genetic factors (i.e., tabaquism, inhalation of toxic fumes, and/or different favoring genes not well identified so far). AAT: Alpha-1 antitrypsin. Pi*: Protease inhibitor. Heterozygosity mainly includes Pi* genotypes MS and MZ.

<table>
<thead>
<tr>
<th>AAT Pi* genotypes</th>
<th>AAT serum levels mg/dL [µM]</th>
<th>Liver polymers accumulation</th>
<th>Risk for liver cirrhosis</th>
<th>Risk for pulmonary emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>100-200 [20-48]</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>MS</td>
<td>100-180 [19-35]</td>
<td>Very slight</td>
<td>No increased</td>
<td>Normal</td>
</tr>
<tr>
<td>SS</td>
<td>70-105 [15-36]</td>
<td>Slight</td>
<td>No increased</td>
<td>*Possible, but not established</td>
</tr>
<tr>
<td>MZ</td>
<td>66-120 [12-35]</td>
<td>Moderate</td>
<td>Increased, but low (~3%)</td>
<td>*Uncertain, but possible in ~10% of subjects</td>
</tr>
<tr>
<td>SZ</td>
<td>45-80 [8-19]</td>
<td>Large</td>
<td>Slightly increased</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>ZZ</td>
<td>10-40 [2-5]</td>
<td>Very large</td>
<td>Highly increased (~25% children; 30% adults)</td>
<td>Highly increased (~60%)</td>
</tr>
<tr>
<td>Null-Null</td>
<td>Not detectable [0.0]</td>
<td>No</td>
<td>No</td>
<td>Greatest risk (practically 100%)</td>
</tr>
<tr>
<td>Z-Null Rare-Null</td>
<td>~10-15 [2-3]</td>
<td>Moderate</td>
<td>Low</td>
<td>Highly increased</td>
</tr>
</tbody>
</table>

Table 1: Serum concentrations of Alpha-1 antitrypsin (AAT) expressed in mg/dL (measured by nephelometry), and micromols (µM), liver accumulation of polymers and risk of liver cirrhosis and pulmonary emphysema development for the different Pi* AAT genotypes (From de Serres and Blanco1, with permission). Values in mg/dL can be expressed in micromolar units (µM) by multiplying its value by 0,1923. Conversion of µM to mg/dL can be done by multiplying its value by a conversion factor of 5.2. *It is necessary the presence of other environmental or genetic factors (i.e., B and/or C hepatitis, non-steroidal anti-inflammatory drugs (NSAIDs) and/or different favoring genes not well identified so far. **It is necessary the presence of other environmental or genetic factors (i.e., tabaquism, inhalation of toxic fumes, and/or different favoring genes not well identified so far). AAT: Alpha-1 antitrypsin. Pi*: Protease inhibitor. Heterozygosity mainly includes Pi* genotypes MS and MZ.

Table 2: Levels of Evidence according to the Oxford (UK) Centre for Evidence-based Medicine (CEBM) (March 2009) [19].

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic reviews (with homogeneity) of randomized controlled trials</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomized controlled trials (with narrow confidence interval)</td>
</tr>
<tr>
<td>1c</td>
<td>All or none randomized controlled trials</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic reviews (with homogeneity) of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study or low quality randomized controlled trials (e.g. &lt;80% follow-up)</td>
</tr>
<tr>
<td>2c</td>
<td>Outcomes Research; ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review (with homogeneity) of case-control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor quality cohort and case-control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, laboratory research or theoretical concepts</td>
</tr>
</tbody>
</table>

Results

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Study 2

A Polish study in 55 patients with CRC analyzed the correlation between antioxidant status and activity of proteolytic enzymes and their inhibitors in cases of colorectal cancer. Total antioxidant status, the levels of lipid peroxidation products (malondialdehyde and 4-hydroxynonenal) and activity of cathepsin G, elastase and their inhibitors (AAT, and alpha-2-macroglobulin) were determined in plasma samples taken before surgery. It was shown that during the development of cancer total antioxidant status was significantly decreased while lipid peroxidation products were increased. Activity of alpha-2-macroglobulin was decreased and activity of...
determined enzymes was not significantly changed. The observed changes indicated a shift in proteolytic-antiproteolytic balance which may enhance carcinogenesis [20]. This pilot study was graded as 4 (insufficient) with the Oxford (UK) Centre for Evidence-based Medicine (CEBM) scale.

**Study 3**

A subsequent population-based case-control study from the Fred Hutchinson Cancer Research Center (Seattle, USA) aimed to evaluate the joint association between smoking and regular non-steroidal anti-inflammatory drugs (NSAID) use with CRC risk, stratified by MSI was conducted in 1,792 CRC cases and 1,501 general population controls from 1998-2002. MSI, defined as MSI high (MSI-H) or MSI low/microsatellite stable (MSI-L/MSS), was assessed in tumors of 1,202 cases. Compared with non-smokers, CRC cancer risk was modestly increased among individuals who had ever smoked. Current NSAID use was associated with a 30% lower risk compared with nonusers. There was a statistically significant interaction between smoking duration and use of NSAIDs. Compared with non-smokers, there was a stronger association within MSI-H tumors with current smoking than there was within MSI-L/MSS tumors. Smokers of long duration were at elevated risk of MSI-H tumors even with NSAID use and smoking. Risk of MSI-L/MSS tumors was not elevated among long-duration smokers with long exposure to NSAIDs but was elevated among long-duration smokers who had never used NSAIDs. Therefore, these findings suggested a synergistic inverse association (implying protection) against colorectal cancer overall as a result of NSAID use and nonsmoking, but risk of MSI-H colorectal cancer remained elevated among smokers even when they had a history of NSAID use [21]. This study was graded as 3b (insufficient) with the Oxford (UK) Centre for Evidence-based Medicine (CEBM) scale.

**Study 4**

Ten years after the first report from the Mayo Clinic Foundation (Rochester, Minnesota, USA), Lindor NM et al., at from the same medical center, re-evaluated the association between AATD and CRC stratified by MSI phenotypes in a larger case-control study. Concordant with prior observations, gender (female) and smoking history were positively associated with colorectal cancers having an MSI-H phenotype. However, no difference in frequency of AAT deficient alleles was found between cases and controls, irrespective of the MSI subtype [16]. This study was graded as 3a (sufficient) with the Oxford (UK) Centre for Evidence-based Medicine (CEBM) scale.

**Study 5**

A recent study from a Spanish group (Asturias, Spain) was conducted in 267 CRC subjects vs. 327 general population healthy subjects, to whom plasma AAT concentration was measured and Pi* genotyping was characterized. This study showed that in addition to the markedly elevated AAT serum levels found in CRC patients, the gene frequency of the severe deficiency Pi*Z allele, and the prevalence of the Pi*MZ, Pi*SZ and Pi*ZG phenotypes were higher in CRC patients than in controls, but these results were inconclusive due to the small sample size [17]. This study was graded as 3b (insufficient) with the Oxford (UK) Centre for Evidence-based Medicine (CEBM) scale.

**Discussion**

There is wide-ranging evidence about the relationship between AATD and the development of various types of malignancy. The level of evidence, in terms of evidence-based medicine, is high with respect to the risk of subjects with Pi*Z allele developing hepatocellular carcinomas [5,6], which reaches the very high percentage i.e. 28%.

Regarding lung cancer, several studies have found Pi*SS, Pi*MS and Pi*MZ individuals to be at increased risk of developing bronchial carcinomas, particularly of the squamous and bronchoalveolar cell
types, independent of smoking habit and presence of COPD [7-11]. The mechanism involved in lung carcinogenesis would be an excess of neutrophil elastase that is not neutralized by AAT and that stimulates development, invasion and metastasis. This same mechanism would possibly be shared by all other types of cancers, including CRC. It is known that both normal and cancer intestinal cells secrete AAT to neutralize elastase [22], which is present in high concentrations in CRC cells, in an attempt to maintain the protease-antiprotease balance, preventing the activation of procathepsin B and proprotein convertase, and reducing production of Tumor Necrosis Factor (TNF) alpha, and Interleukin-1a, which in turn prevents liver metastases [23-25]. There is also some evidence of a relationship between AAT deficiency and the development of neoplasms of the urinary bladder, gallbladder, and malignant lymphomas [12-14].

Of note, there is a documented association of AATD and ulcerative colitis (UC) [26]. On the one hand, a recent retrospective large study from the UK Registry of patients with severe AATD confirmed a higher prevalence of UC than would be expected in the general population, providing further evidence of a potential link between these two conditions [27]. On the other hand, it is generally accepted that the risk of CRC is increased among patients with UC, and thus screening for CRC and its precursor, dysplastic lesions, has universally been recommended in long-standing, extensive colitis [28,29]. Therefore, in theory AATD could be a modifier genetic factor that favors the development and increases the UC severity, and secondarily CRC development. However there are not published studies on the prevalence of CRC in patients with AATD and UC.

The relationship between AATD and CRC is a controversial subject little studied. Really in the present analysis the level of evidence found on this relationship is very weak, with only a study providing a 3a level of evidence [16] and all other 3b and 4 levels [15,17,20,21], according to the 2009 Oxford CEBM guidelines [19].

However, the current analysis has some remarkable limitations due to the limited available and reliable published material on the chosen topic. These limitations are a significant obstacle in finding a trend and a meaningful relationship between CRC and AATD, but also an opportunity to make suggestions for further research, since a new key objective of the research process is not only discovering new knowledge but to also confront assumptions and explore what we don't know [30].

In summary, although the scientific level of the existing evidence on the relationship between AAT and CRC is currently low, the available studies (some of them with conflicting data), do not allow either acceptance or dismissal this supposed relationship. Further studies would be needed to clarify this issue.

References


