Genetic polymorphisms of Cox enzyme 
and risk of colon adenoma and adenocarcinoma: 
A systematic review

Ana F. Lima (med06167@med.up.pt); Ana T. Pinheiro (med06189@med.up.pt); Hugo A. Macedo (med06018@med.up.pt); Filipa B. Fernandes (med06012@med.up.pt); João A. Coimbra (med06039@med.up.pt); Lúcia E. Guedes (med06060@med.up.pt); Mara V. Fernandes (med06233@med.up.pt); Miguel P. Freitas (med06095@med.up.pt); Patrícia M. Marques (med06102@med.up.pt); Rui F. Castro (med06121@med.up.pt); Sara S. Gouveia (med06236@med.up.pt); Telma A. Brito (med06145@med.up.pt); Mário Dinis Ribeiro (mario@med.up.pt)

Prof. Doutor Altamiro Costa Pereira (altamiro@med.up.pt)

Abstract

Introduction. Colon adenocarcinoma is one of the major causes of death in Portugal. Cox enzymes, are produced in response to inflammation in precancerous and cancerous tissues. It was though that Cox polymorphisms could be related to the appearance of polyps and a possible future cancer in the region mentioned.

Aim. Our aim was to estimate the effects of Cox polymorphisms on colon adenoma and adenocarcinoma.

Methods. A systematic review was performed gathering seven full articles obtained after applying inclusion and exclusion criteria by different reviewers on abstracts and full texts from Medline and Scopus databases (abstracts=69; articles=13). Variables we defined referred to different types of study, regions, ethnic groups and quality (using STROBE).

Results. From the seven articles, five were case-control and two were cohort. Several ethnic groups were studied. Quality evaluation had a mean of 27 (a minimum 22, a maximum 33) out of 38. For the risk of adenoma, using polymorphism 768, 5229, 8494, R&W, L15-L16del, P17L and L237M, OR= 0,92 with a 95% confidence interval [0,84;1,02] and p value for heterogeneity<0,00001. Polymorphism P17L and L15-L16del have the most significant results, P17L has the biggest protective effect and L15-L16del has the higher effect of risk. For the risk of adenocarcinoma, using polymorphisms PTGS2.926, PTGS2.401, PTGS2.1629, PTGS2.3050, PTGS2.5209, PTGS2.8473, PTGS2.9850 and PTGS2.10335, OR=1,12 [0,98;1,29] and p value for heterogeneity=0,009. Polymorphisms PTGS2.9850 and PTGS2.401 have the most significant results PTGS2.9850 has the highest effect of risk and PTGS2.401 has the most protective effect.

Conclusion. Any conclusion on the risk of adenoma or adenocarcinoma related to Cox polymorphisms is precocious. The heterogeneity found may be related to differences in function of polymorphisms and types of study. Further studies with adequate design should address to the polymorphisms with the most significant results.

Keywords: Cox enzymes, polymorphism, adenocarcinoma, adenoma, colon, risk.
Introduction

Cancer is a major subject nowadays. It is the second leading cause of death worldwide. In Portugal, colon adenocarcinoma represents the second cause of cancer that causes deaths [see figure 1] (mortality rate is 20/100,000 in male and 11/100,000 in female) [1].

The colon hosts the more primary neoplasms than any other organ in the body. Cells begin growing in an uncoordinated manner and when a tumorous mass projects above the mucosal surface forming a macroscopically visible structure there is a polyp [1].

Adenomas are neoplastic polyps that range from small tumours to large lesions. Adenocarcinomas are malignant neoplasms of epithelial cells [1]. This means that normal tissue can evolve into an adenoma that eventually develops to an adenocarcinoma.

Mutations rate increases in both male and female subjects with age due to environmental and genetic factors. Males are the most affected after the age of 45 [see figure 2]. Besides getting higher with age, this rate is also influenced by epidemiologic factors that people are submitted to, everyday, such as coffee, alcohol, nutrients, tobacco or exercise, that also have an influence on this rate [3,4,5,6]. Genetic variation namely polymorphisms may explain interindividual differences in inflammation response.

Cox enzymes (cyclooxygenase enzymes), also known as prostaglandin H2 synthase (PTGS) enzymes, convert arachidonic acid to prostaglandin H$_2$, a precursor to all prostanoids [7,8,9,10], and are produced in the organism in response to inflammation in

![Fig. 1- Cancer rate distribution in Portugal: in male colon cancer has the second highest rate of incidence and third highest rate of mortality. In female, colon cancer has the second leading rate of both incidence and mortality. Moreover, the rates of incidence and mortality are higher in male. Information obtained from IARC [2].](image1)

![Fig. 2- Cancer rate and aging: until the age of 45, female subjects have higher incidence rates of colon cancer. Male subjects have the highest after the 45. However, in both male and female subjects this rate increases with age due to genetic and epidemiologic factors. Information obtained from IARC [2].](image2)
precancerous and cancerous tissues. [1]. There are two forms of human Cox, Cox1 and Cox2. They are similar in structure but encoded by different genes. Both are located in the nuclear envelope and endoplasmic reticulum of cells, even though Cox2 is absent from many cells unless induced by tumor promoters, growth factors or cytokines. Cox1 is involved in cell signaling. Cox2 occurs in high levels in colon cancer. [7,8,9,10]

Our aim is to estimate the risk of colon adenoma or adenocarcinoma among individuals with Cox polymorphisms.

**Methods**

A systematic review was performed. Observational studies, namely, cohort studies and case-control studies were the ones included to evaluate the risk of adenomas or adenocarcinomas with or without the presence of Cox polymorphisms.

**Papers selection**

The paper selection was made by introducing specific queries in different data bases. After applying the queries in Medline and Scopus we reached a total of 69 abstracts [see table 1 and 2].
Inclusion and exclusion criteria definition and application

The abstracts found were then submitted to the inclusion and exclusion criteria.

The inclusion criteria chosen were observational studies relating Cox polymorphisms with colon cancer or adenoma. The exclusion criteria chosen were: studies focused in non-human subjects and studies in languages besides English, French, Spanish or Portuguese. The single limit imposed in the search was the date of the abstracts obtainment, November 2006.

All 69 abstracts, with no exception, were read by two people so that the criteria were applied independently. In the end, 46 abstracts were excluded because they weren’t written in English, French, Spanish or Portuguese or had non-human subjects, leading to a total of 13 abstracts. After obtaining the full texts, four groups of three people were defined to read the articles available and obtain the information required for the study. 6 articles [11,12,13,14,15,16] were not included in our work because Cox polymorphisms were not mentioned specifically and were not related to colon adenoma and adenocarcinoma, reaching a number of 7 articles included [17,18,19,20,21,22,23] [see figure 3].

Fig. 3- Description of the methods performed during the work progress. From the 69 abstracts obtained, 46 were not included. 13 full texts were analysed and 6 of them were excluded, ending up with 7 articles included. (n=abstracts and N=articles).
Variables Definition

The articles were then fully read and specific data was extracted [see table 3] Three people were chosen to evaluate the articles included (n=7). Tables provided by STROBE with several items of evaluation were filled.

Tab. 3- Variables extracted from articles

<table>
<thead>
<tr>
<th>Publication</th>
<th>Variables</th>
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</thead>
<tbody>
<tr>
<td>- Title</td>
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<td>- Authors</td>
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<tr>
<td>- Journal</td>
<td></td>
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<tr>
<td>- Year of publication</td>
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</table>

<table>
<thead>
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<th>Variables</th>
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</thead>
<tbody>
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<tr>
<td>- Selection methods</td>
<td></td>
</tr>
<tr>
<td>- Quality</td>
<td></td>
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<table>
<thead>
<tr>
<th>Settings</th>
<th>Variables</th>
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<tr>
<td>- Gender distribution</td>
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<tr>
<td>- Location of the study</td>
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<td>- Ethnic origin</td>
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</table>

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Variables</th>
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</thead>
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<tr>
<td>- Polymorphism</td>
<td></td>
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<tr>
<td>- Laboratory methodology</td>
<td></td>
</tr>
</tbody>
</table>

Tab. 3- Different variables used to extract data from the 7 articles included. We defined several variables considering the publication, studies, settings and procedures

Data Base Creation

The information was gathered on an electronical data base through SPSS 14.0 and Review Manager 4.2.

In SPSS we did the principal table of data using the articles and the analyses of the articles’ quality table. At the end an output and syntax were obtained.

Through Review Manager we gathered all the data from the included articles and using forest plots for both risk of adenoma and risk of adenocarcinoma, we reached a value OR for risk of adenoma and risk of adenocarcinoma.

Results

Description of included articles

The information resulting by the analyses of the articles considering the publications, studies and quality evaluation is shown on Table 4.
Tab. 4- Information of the publications, studies and quality of the articles

<table>
<thead>
<tr>
<th>Type of study</th>
<th>n</th>
<th>Male (%)</th>
<th>Age (mean)</th>
<th>Ethnic Groups</th>
<th>Laboratory methodology</th>
<th>Polymorphism</th>
<th>Quality (out of 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sansbury L, 2006</td>
<td>566</td>
<td>48</td>
<td>-</td>
<td>Caucasian</td>
<td>PCR</td>
<td>-</td>
<td>27</td>
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<tr>
<td>Ali I, 2005</td>
<td>1455</td>
<td>69</td>
<td>-</td>
<td>-</td>
<td>PCR</td>
<td>Poli-768; -5229; -8494</td>
<td>22</td>
</tr>
<tr>
<td>Ulrich C, 2005</td>
<td>1264</td>
<td>-</td>
<td>-</td>
<td>Americans</td>
<td>Genotyping</td>
<td>-</td>
<td>24</td>
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<tr>
<td>Moreno V, 2004</td>
<td>566</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>PTGS2.401; 926; 1629; 3050; 5209; 8473; 9850; 10335 R&amp;W; L15-L16del; P17L; L237M</td>
<td>29</td>
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<tr>
<td>Ulrich C, 2004</td>
<td>1487</td>
<td>46</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>31</td>
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<tr>
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<td>60</td>
<td>Chinese</td>
<td>PCR</td>
<td>-</td>
<td>23</td>
</tr>
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<td>Lin H, 2002</td>
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<td>49</td>
<td>63</td>
<td>Various</td>
<td>PCR</td>
<td>-</td>
<td>33</td>
</tr>
</tbody>
</table>

Type of study= classification of the study design; n= total participants number; Male (%) = percentage of male; Age (mean) = mean age in years; Ethnic group= different ethnic groups; Laboratory methodology= techniques of cellular biology used in labs; Polymorphism= identification of the polymorphisms; Quality= total number of points obtained by the quality evaluation (out of 38).

There we could analyze and compare the different variables of all the articles.

The total number of individuals in all the studies performed and selected was 6860.

The articles selected were published between 1998 and 2006, being three from 2004, two from 2005, one from 2006 and one from 2002. Four of the articles had no mention to more than one ethnic group. Five articles presented case-control studies and two of them cohort studies.

In Review Manager we differentiated various types of polymorphisms mentioned in all the articles. The ones that did not specified the polymorphism studied was not estimable and so was excluded from our values so that it would not interfere with our interpretation of the results.

Three groups of variables were compared: adenoma vs. normal, adenocarcinoma vs. normal and adenocarcinoma vs. adenoma. Only the first two were effective because we did not have enough information to compare the variables adenocarcinoma and adenoma.
Risk of adenoma

Considering these variables, we compared seven polymorphisms (poli-768, poli-5229, poli-8494, poli-8494, R&W, L15-L16del, P17L and L237M) from two articles [18,19].

Polymorphism L15-L16del has the highest effect of risk and P17L has the biggest protective effect.

The value of OR for total was 0.92 with a 95% confidence interval [0.84;1.02]. We might conclude that these polymorphisms have a protective effect for the presence of adenomas but it is not a significant value and moreover, for the heterogeneity test $p<0.00001$, which means that the results from all the polymorphisms were not synchronized with each other so we were not able to conclude for the generality [see figure 4].

![Fig. 4- Forest plot for risk of adenoma.](image)

Polymorphism L15-L16del has the highest risk effect and P17L has the biggest protective effect.
Risk of adenocarcinoma

Considering this values we compared eight polymorphisms (PTGS2.401, PTGS2.926, PTGS2.1629, PTGS2.3050, PTGS2.5209, PTGS2.8473, PTGS2.9850 and PTGS2.10335) from one article [20].

Polymorphism PTGS2.9850 has the highest effect of risk and PTGS2.401 has the most protective effect.

The value of OR for total was 1.12 with a 95% confidence interval [0.98-1.29]. This value may lead us to conclude that these polymorphisms have a effect of risk but this value is not significant considering the confidence interval and for the heterogeneity test p = 0.009 so the results are not constant enough to make it possible to conclude for generality [see figure 5].

![Fig. 5- Forest plot for risk of adenocarcinoma.](image)

Polymorphism PTGS2.9850 has the highest effect of risk and PTGS2.401 has the biggest protective effect.
Discussion

This study was performed with the purpose of finding if polymorphisms related with Cox enzymes, found in patients, could indicate risk of colon adenoma or colon adenocarcinoma. Our goal was to gather the information, available in published articles of studies performed by several researchers in different conditions, and try to obtain a general conclusion from all the articles. That way it would be possible to transport these concepts to the clinic and allow doctors to make a more perfect diagnose and prevent a cancer or prescribe a treatment at an early stage.

Our limitations range from the fact that we found different polymorphisms with different functions. In order to overcome this barrier we could have searched for more information on each single polymorphism to relate it to the aim of our work.

There were also some difficulties during all the process. Firstly we had few articles suitable. Secondly the polymorphisms mentioned were not in common, which led to certain heterogeneity. A better study on this subject could be made if we had developed an analysis on a single polymorphism.

To sum up, our annual work was productive because we reached the aim of our work. However, the results were not conclusive so we can not say that Cox polymorphisms are either risky or protective for colon adenoma or adenocarcinoma.

However the most significant results were: polymorphism P17L with the highest protective effect and L15-L16del with the higher effect of risk for risk of adenoma. Polymorphism PTGS2.9850 has the higher effect of risk and PTGS2.401 has the most protective effect for risk of adenocarcinoma.

Further studies with adequate design should address specially to the polymorphisms with the most relevant results.

References

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