Author’s response to reviews

Title: Molecular Pathways Undergoing Dramatic Transcriptomic Changes During Tumor Development in the Human Colon

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Version: 4 Date: 28 November 2012

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Dear Editor,

In the enclosed revision of our manuscript, we have done our best to address Reviewer 2's latest comment. We would like to point out, however, that the information requested was (and is) already present in the manuscript. Indeed, the strong correlation between the size and histological features of precancerous colon lesions, which has been well-established for years, was clearly confirmed in our series. Our decision to focus on size alone was also based on technical and statistical considerations.

We have attempted to clarify this issue once and for all in the revised text. We hope our efforts will be sufficient to allay the reviewer's doubts and that this time the review process can be completed more rapidly.

Best regards,

Giancarlo Marra and Nicola Ancona.

Response to Reviewer #2 (Dr. Pablo Conesa-Zamora)

Major compulsory revision

This study is, to a major extent, confirmatory of previous works. The authors should include an analysis in which villous component and grade of dysplasia along with size are taken into account in order to classify the polyps. The already performed analysis in which only size was taken into account could be complementary to this proposed analysis.

It is well-known that the size of precancerous colon lesions displays strong positive correlation with histologic features like villous changes and high-grade dysplasia. Table 1 (the same table included in the original and revised versions of our manuscript) clearly illustrates this correlation: 43.5% of the larger precancerous lesions included a villous component (vs. 36.8% of the smaller lesions), and 34.8% had high-grade dysplasia (vs. 10.5% of the smaller lesions).

Because the correlation between size and histology is well-established and the number of lesions analyzed was limited, we decided to focus our analysis on the former variable. Classifying lesions on the basis of villous changes or degree of dysplasia would have resulted in smaller groups, and the statistical power of our analysis would have diminished. In addition, it would have been impossible to identify the predominant histologic
component (e.g., villous or tubular) in the endoscopic fragments we homogenized for RNA extraction and microarray analysis—or rather, this would have been possible with tissue microdissection, but this procedure can diminish the quantity and quality of the extracted RNA.

As we explained in our previous response to the reviewer (Point 2), the size of precancerous lesions is a reliable indicator of their advancement in the transformation process. It is true that some small lesions are already invasive, but these are usually nonpolypoid (often depressed). In any case, small invasive lesions are the exception to the rule: larger lesions are more advanced on the road to cancer.

In conclusion, we have added a sentence on page 8 (end of the first paragraph), which highlights the correlation between size and histology and will hopefully clarify this point for readers.

Sentence in the manuscript:
As expected, LPLs were more likely to exhibit villous changes (43.5% vs. 36.8% of the SPLs) and high-grade dysplasia (34.8% vs. 10.5% of the SPLs).