Reviewer 1

1 Data of clinical manifestation are inadequate for this cohort of patients. Although this study is retrospective, history of familial polyposis for these patients should be described briefly.

As suggested, an additional table was enclosed in revised manuscript reporting a series of demographic and clinical characteristics of enrolled patients including their history of familial polyposis.

2 A table is suggested to list the basic clinical characteristics of this cohort.

As reported in previous answer, the table has been added in the new version of the manuscript.

3 Patients with "dyspeptic symptoms" should not be described as "healthy", and the endoscopy for them might be to detect insidious lesions. Selection of the cite and number of biopsy must be described.

Controls were selected from archive material. At least two biopsy samples had been taken in subjects undergoing upper endoscopy for dyspeptic symptoms from the second duodenum. The absence of both histological and endoscopic abnormalities in this site was the main criteria of selection. Moreover, a further confirmation of a normal duodenal picture was based on the presence of less than 10 CD3/100 enterocytes by immuno-histochemical staining. Finally, in all patients, possible causes of "Duodenal lymphocytosis" had been excluded according to a previous report from our group (Losurdo et al, World J Gastroenterol, 2015, reference n. 18).

4 There are typo and grammatical errors in the manuscript.

Linguistic revision was performed by a mother tongue speaker.

Reviewer 2

This paper is well written and the work was well done. The results are very interesting and bring new important knowledges in adenomatous polyposis.

We thank the reviewer for his kind evaluation of the paper.

Reviewer 3

The authors investigate the expression of ERs in FAP duodenal carcinomas and their relationship with epithelial proliferation and apoptosis markers. They found that that ER-beta strongly decreases in duodenal FAP carcinomas in a multiple step way with a putative anti-carcinogenetic effect. ER-alpha has an opposite trend. Overall, the paper is well-written. I have the following comments:

1) The major limitation of this study is its small sample size, which needs to clarify in the discussion section

We agree that the sample size is small. However, we need to take into account the rarity of FAP (incidence ranges from 1:7000 to 1:8000 births per year; references n. 2 and 3) and, even more, of its localization in the small bowel (8.5% of FAP patients in a registry study of 1255 patients with FAP; Jagelman DG, De Cosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet 1988; 1:1149–51, reference n. 36). On the other hand, all studies regarding duodenal FAP enclose a similar number of cases at the best of our knowledge (ref. 37-39.

2) The previous studies on the similar issue should be mentioned, and possible explanations turnover on the relationship between ERs and cellular are needed to be provided in detail.

Despite similar studies have been performed in colo-rectal localization of FAP (references n. 14 and 30 from our group), no similar studies are available with regard to duodenal localization. In this site, only one clinical study, showing that ER-beta agonists are able to reduce number and size of duodenal polyps in FAP, deals with this subject (reference n. 16). Our findings demonstrate that: i) a deep ER-beta decrease is evident in the progression from normal tissue to neoplasm; ii) ER-beta expression is directly related to apoptosis expressed as TUNEL LI; iii) the co-expression of ER-beta and caspase 3 undergoes a strong decline from normal to neoplastic tissue. The data provide a possible explanation of the relationship between ERs and cellular turnover.