

Reviewer (1)

This is a good clinical trial, congratulations.

Reviewer (2)

Authors

The paper is scientifically accurate, complete and fully comprehensive to the reader. The reference section is adequate, up-to-date and appropriate to back up the points made in the article. The study conveys a clear-cut message. I have no major comments on this paper. **There are a point that need to be addressed: the author should implement the discussion on colorectal cancer methylation on the basis of the paper “Kaz AM, Wong CJ, Dzieciatkowski S, Luo Y, Schoen RE, Grady WM. Patterns of DNA methylation in the normal colon vary by anatomical location, gender, and age. Epigenetics. 2014 Apr;9(4):492-502. doi: 10.4161/epi.27650”.**

Comments:

I would like to thank my colleague for his comments and advice. I have referred to this study in the text. It is reference number (43) at present. But I cannot implement the findings of this report in the discussion of my review. In my review, I have discussed a correlation between a specific environmental risk factor and the development of colorectal cancers in young persons and I could not find any useful relevant information that could be added to my report.

Reviewer (3)

Nice organization and good viewpoint on water pollution and CRC, the paper should be useful in public hygiene on CRC prevention. Minor: 1) **Could be explained a little more in the context with references on “the relationship between oestrogen functions in diminishing the possibilities of such risk by reducing the entrance of and enhancing the elimination of these xenobiotics”** 2) If “Hypo-methylation of genomic DNA and screening for CRC” is closely related to the topic of water pollution and CRC, **better expressed in more detail.** 3) In “Discussion and conclusion”, water chlorination, oestrogen and DNA Hypo-methylation should be better logically connected.)

Comments:

Thank you for your comments. To address the requirements of point (1) above, I have added to the text reference number (32). For addressing point (2) above, I have added references (32) and (43) to the text. The recommendation in point (3) above necessitates conducting specific studies for addressing this topic.

Reviewer (4)

Overall, this is a good and useful review article. Please improve following points. Especially, many quoted papers are old reviews, which no one will read. References need to be improved. Since this review focuses on exposures (environment and medications) and cancer risk, **discussion on effect of exposures on carcinogenic mechanisms is essential.** ⁽¹⁾ Hence, this review must discuss integrative science of "molecular pathological epidemiology". This idea of molecular pathological epidemiology has been written in the literature (eg, S Ogino et al. Gut 2011; PT Campbell et al. Cancer Epidemiol Biomarkers Prev 2015; S Ogino et al. Cancer Causes Cont 2015; R Nishihara et al. Eur J Epidemiol 2015.) Other papers which should be added and discussed include as follows: Molecular pathways **D Colussi et al. Int J Mol Sci 2013** ⁽²⁾ K Bardhan et al. Cancers 2013 **JM Ng et al. Int J Mol Sci 2015** **Hormone use and molecular markers**⁽⁴⁾ **JH Lin et al. Cancer Res 2012.**⁽³⁾ **F Caiazza et al. Front Oncol 2015** ⁽⁵⁾

Comments:

1. Thank you for your comments. For addressing point (1) above, I have added references (32) and (43) to the text.
2. But the Report of Colussi and others is irrelevant to my Manuscript as I am discussing a possible correlation between the exposure of specific environmental risk factor and the development of colorectal carcinoma. For reference, please review the box below.

Dora Colussi 1, Giovanni Brandi 2, Franco Bazzoli 1 and Luigi Ricciardiello 1,*
Molecular Pathways Involved in Colorectal Cancer: Implications for Disease
Behavior and Prevention. Int. J. Mol. Sci. 2013, 14, 16365-16385;
doi:10.3390/ijms140816365

[Abstract: Research conducted during the past 30 years has increased our understanding of the mechanisms involved in colorectal cancer initiation and development. The findings have demonstrated the existence of at least three pathways: chromosomal instability, microsatellite instability and CpG island methylator phenotype. Importantly, new studies have shown that inflammation and microRNAs contribute to colorectal carcinogenesis. Recent data have demonstrated that several genetic and epigenetic changes are important in determining patient prognosis and survival. Furthermore, some of these mechanisms are related to patients' response to drugs, such as aspirin, which could be used for both chemoprevention and treatment in specific settings. Thus, in the near future, we could be able to predict disease behavior based on molecular markers found on tumors, and direct the best treatment options for patients]

3. Likewise, the report of **JH Lin et al. Cancer Res 2012** is also irrelevant. [Postmenopausal Hormone Therapy Is Associated with a Reduced Risk of Colorectal Cancer Lacking CDKN1A Expression] [our molecular pathological epidemiology findings suggest a preventive effect of hormone therapy against colorectal

carcinogenesis that depends, in part, **on loss of cyclin-dependent kinase inhibitor CDKN1A]**

4. I have added the report of Caiazza et al. It is the reference number (15)

Reviewer (5)

The manuscript reviews current data on the role of chlorinated water on the potential development of colorectal cancer. It is well structured and well referenced and gives a clear overview of the field.