Reviewer's report

Title: Use of various HRT formulations is not associated with increased risk of colon cancer: A case-control study

Version: 2 Date: 27 March 2007

Reviewer: Angiolo Gadducci

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General
The possible protective role of estrogens in colon carcinogenesis has been long debated. ER-alpha e ER-beta have been detected in normal colon in both sexes. ER-beta is the predominant ER-subtype in the human colon, and decreased levels of ER-beta-1 and ER-beta-2 mRNA are associated with colonic tumorigenesis in females. ER gene is methylated in 90% of colon cancer tissues. Methylation of DNA is equivalent to gene silencing, with inactivation of a number of genes downstream. Methylation-associated inactivation of the ER gene in aging colon rectal mucosa could be one of the earliest events in colorectal carcinogenesis. In vitro estrogens reduce the ER-gene methylation and inhibit cell proliferation. Moreover, estrogens have been shown to increase the expression of vitamin-D receptors in a variety of tissues. 1,25-dihydroxyvitamin D and several of its analogs are potent antineoplastic and pro-differentiative agents in several cell types, including colon-derived cells. The increased vitamin-D receptor activity may be one of the mechanisms by which estrogens can protect against colon carcinogenesis. Because of the small numbers of cases in many sub-analyses, the authors failed to detect meaningful differences in colon cancer risk according to different hormone preparations or ways of administration.

Specific questions.

The authors found that ever -oral contraceptive users had a significant reduced colon cancer risk when compared to never users (OR = 0.64, 95% CI, 0.46-0.89). Conversely, no significant difference in colon cancer risk was detected between ever- HRT users and never users. Have the authors a biological explanation for this discrepancy?

Have the authors found any difference in right colon cancer and left colon cancer risk associated with HRT use?

Have the authors found any correlation between HRT use and colon cancer mortality?

--------------------------------------------------------------------------------------------------------------------------------- Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

--------------------------------------------------------------------------------------------------------------------------------- Discretionary Revisions (which the author can choose to ignore)
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What next?: Accept without revision

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I have no competing interests.