Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis
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Authors' objectives
To evaluate the effect of postmenopausal hormone use on the risk of colorectal cancer in women.

Searching
A computer search of the MEDLINE database (January 1966 to September 1998) and a review of the references was undertaken to identify English-language articles. The search was undertaken using the MeSH terms 'colorectal, colon, and rectal neoplasm' or textword terms 'colorectal, colon, and rectal cancer' combined with the MeSH terms 'estrogen, estrogen replacement therapy' or textword terms 'hormone replacement therapy, postmenopausal hormones, noncontraceptive hormones'.

Study selection
Study designs of evaluations included in the review
Observational studies that included quantitative data. Studies that included preliminary analyses that were superseded by more recent publications from the same study sample were excluded.

Specific interventions included in the review
Post-menopausal hormone therapy, including combined hormone therapy (estrogen and progestin) and tamoxifen. Studies where there was no clear distinction between the use of oral contraception and post-menopausal hormone, or where the definition of hormone use was unclear were excluded. Separate analyses were performed within categories of hormone use (ever use, current use and duration of current use) and cancer type (colon cancer, rectal cancer, colorectal cancer). Included studies used several cut off points for duration of hormone use (e.g. 4, 5, and 6 years).

Participants included in the review
Postmenopausal women. Pre-menopausal women were excluded from the analysis where possible.

Outcomes assessed in the review
Estimates of the risk of cancers of the colon or rectum in relation to postmenopausal hormone use.

How were decisions on the relevance of primary studies made?
Articles were reviewed by two unblinded reviewers to determine eligibility.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted from the review, or how many of the reviewers performed the data extraction. For each individual study the odds ratios (ORs), relative risks (RRs) and the 95% confidence intervals (CIs) were abstracted. Estimates were adjusted for multiple confounding factors when available.

Methods of synthesis
How were the studies combined?
The weighted average of the estimated RRs was calculated by giving each study a weighted proportion to it's precision. Summary RR estimates and 95% CI were calculated using a general variance-based method based on a fixed-effect
model; summary effects from a random-effects model were reported to be quite similar.

How were differences between studies investigated?
Test for heterogeneity were used to evaluate the consistency of findings among studies.

Results of the review
Eighteen epidemiologic studies of postmenopausal hormone therapy and colorectal cancer were included (n>5197). Four studies that investigated the association of hormone therapy and colorectal adenoma (n>1695) were also included and four studies that investigated the use of tamoxifen (n>85,411).

Thirteen out of 18 studies reported lower risks of colon cancer for ever users of postmenopausal hormones that nonusers (RR 0.80, 95% CI: 0.74 to 0.86). However, there was significant heterogeneity among the studies (p=0.02). When five studies in which premenopausal women were part of the reference group of never users were excluded the summary RR was 0.76 (95% CI, 0.70 to 0.82) and there was no heterogeneity among the studies (p=0.32).

Ten studies investigated the relation between ever using postmenopausal hormone therapy and cancer of the rectum. The summary RR was RR 0.81 (95% CI: 0.72 to 0.92), and there was significant heterogeneity among the studies (p=0.03). When studies that were not strictly of postmenopausal women (n=3) were excluded the summary RR was unchanged (RR 0.81), but the test for heterogeneity was of borderline significance (p=0.06).

For current postmenopausal hormone use the data on colon and rectal cancers were combined. Of the ten studies with data on current hormone use, RR 0.66, 95% CI: 0.59 to 0.74. There was no evidence of heterogeneity among the studies (p=0.89).

Five studies provided data on the duration of current use. Summary RRs were: short duration RR 0.61, 95% CI: 0.48 to 0.79; long duration RR 0.67, 95% CI: 0.56 to 0.79).

Only four investigations were found to have examined postmenopausal hormone therapy and colorectal adenomas. Three reported significant results where the incidence of adenoma was lower among women taking or having ever used postmenopausal hormone therapy. It is not clear why a summary RR was not presented.

Although data are sparse, preliminary evidence suggests that bowel cancer incidence may be increased among women taking tamoxifen therapy, which has both estrogenic and antiestrogenic effects. No association was found between combined estrogen and progestin use and colorectal cancer

Authors’ conclusions
Observational evidence, as well as some biologic evidence, suggests that postmenopausal hormone replacement may reduce the risk of colorectal cancer. Women and their physician may want to consider this apparent protection, along with the other benefits and risks of postmenopausal hormone therapy, in deciding to use hormones.

CRD commentary
The review states an objective and predefines inclusion and exclusion criteria. MEDLINE was the only electronic database that was searched and therefore some important information may have been missed. No attempt was made to look for unpublished data and only English language papers were considered for inclusion (papers with significant findings may be more likely to be published in English), therefore publication bias cannot be ruled out. Information about the methodology of the review process (whether more than one reviewer conducted data extraction and how discrepancies were resolved) was limited and there was no reported validity assessment of included studies.

The authors conclusions seem to follow from the results presented.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.
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**Other publications of related interest**
This additional published commentary may also be of interest. Jagadeesan UB. An incentive to start hormone replacement: the effect of postmenopausal hormone replacement therapy on the risk of colorectal cancer. JAGS 2002;50:768-70.

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**Record Status**
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