The effect of estrogen vs combined estrogen-progestogen therapy on the risk of colorectal cancer
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CRD summary
The authors concluded that overall there was consistent evidence to support an association between oestrogen-progestogen therapy and colorectal risk reduction. The analyses suggested that only current use of oestrogen therapy was associated with a decreased risk of colorectal cancer. The authors conclusions reflect the evidence presented but their reliability is uncertain due to methodological weaknesses in the review.

Authors' objectives
To compare the effect of oestrogen and combined oestrogen-progestogen therapy on the risk of colorectal cancer in perimenopausal or postmenopausal women.

Searching
PubMed and EMBASE were searched for relevant studies published up until September 2010. Search terms were reported. No language restrictions were reported. Key review articles and reference lists of identified records were checked for potentially eligible studies.

Study selection
Studies that investigated the effect of oestrogen therapy or combined oestrogen-progestogen therapy in perimenopausal or postmenopausal women were eligible for inclusion. Study endpoints had to be colorectal cancer, colon cancer or rectal cancer with sufficient data presented to calculate relative risk (RR) and its standard error. Studies that investigated the association between oral contraception and colorectal cancer in young women and studies that used non-specific or mixed hormone therapies were excluded.

Mean participant age was reported for one study (54.5 years); other studies had age inclusion criteria that ranged from 20 to 79 years (where reported). One study was published in 1979 and the others were published between 1995 and 2010. Fifteen studies were conducted in North America and five in Europe. Most studies assessed the incidence of colorectal cancer alone. Other studies investigated colon cancer, rectal cancer or a combination of these outcomes. Most studies evaluated oestrogen therapy and combined oestrogen-progestogen therapy and some also included progestogen alone. Other studies evaluated oestrogen therapy only or combined oestrogen-progestogen therapy only. Various exposure variables were assessed: ever use (had the participant ever received hormone therapy), recent use (variable definitions) and duration of use.

It was not reported how many reviewers selected studies for inclusion.

Assessment of study quality
Information on quality-related characteristics were recorded during data extraction. All articles were assessed for confounding, selection and information bias.

Data extraction
Data were extracted from each study on ratios of cumulative incidence, incidence rates and odds of developing colorectal cancer to calculate relative risks, estimated with 95% confidence intervals (CIs).

Two reviewers extracted data and these were checked by a third reviewer.

Methods of synthesis
Pooled relative risks and 95% CIs were calculated with a random-effects model. Heterogeneity was assessed using the Q test and \( I^2 \) statistic. Studies were further analysed with a meta-regression. Subgroup analyses were performed based on population and study criteria. The possibility for publication bias was investigated using Begg's and Egger's tests.
Results of the review

Twenty studies were included in the review (458,676 participants): four randomised controlled trials (RCTs) (30,278 participants), eight cohort studies (400,934 participants) and eight case-control studies (27,464 participants). Sample sizes ranged from 168 to 94,505; most studies contained several thousand participants. Follow-up time (where reported) ranged from 3.2 to 15 (units not reported).

Ever use of oestrogen therapy was associated with a decreased risk of colorectal cancer (RR 0.74, 95% CI 0.68 to 0.81; 17 studies) as was ever use of combined oestrogen-progestogen therapy (RR 0.79, 95% CI 0.69 to 0.91; 14 studies). There was evidence of significant heterogeneity for the oestrogen only analysis (I²=69.2%). When studies were pooled there were no significant differences between oestrogen therapy and combined oestrogen-progestogen therapy for risk of colorectal cancer.

Current use of oestrogen therapy had a significantly lower risk of colorectal cancer (five studies) compared to former use (five studies). There were no significant differences between current (five studies) and former (five studies) use of combined oestrogen-progestogen therapy.

Risk of colorectal cancer was lower than risk of rectal cancer for both oestrogen therapy and combined oestrogen-progestogen therapy, but this difference was not statistically significant.

Other subgroup analyses were reported. Sensitivity analyses did not significantly alter the overall results. There was no evidence of publication bias.

Authors’ conclusions

Overall there was consistent evidence to support an association between oestrogen-progestogen therapy and colorectal risk reduction. The analyses suggested only current use of oestrogen therapy was associated with a decreased risk of colorectal cancer.

CRD commentary

The review question was clear. Inclusion criteria were reported. It was unclear whether all women in the included studies were perimenopausal or postmenopausal. Some relevant databases were searched for eligible articles. It was not reported whether a language and publication restrictions were applied, so the risk of eligible studies being missed was unclear. It was unclear whether appropriate methods (such as independent duplicate processes) were used to minimise the possibility of reviewer error and bias during study selection. Appropriate processes were reported for data extraction and quality assessment.

Quality assessment of included studies was incorporated into data extraction, but the results of this assessment were not reported clearly and the reliability of the included studies remained unknown. Differences in study design were accounted for in subgroup analyses, but combining studies of different designs in a meta-analysis may not have been appropriate. Appropriate trial details were reported. Participant age was not reported consistently, which made it difficult to assess the appropriateness of the investigated women for the therapy under investigation. Reporting of results was somewhat unclear for the benefit or harm of oestrogen therapy compared to combined oestrogen-progestogen therapy. Suitable measures were used to assess heterogeneity.

The authors conclusions reflect the evidence presented, but the reliability of the conclusions is uncertain due to lack of clarity of the included participants, missing detail on study quality and combining studies of different designs.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors recommended that further studies explore the underlying biological mechanisms of the effect of hormone therapy on colorectal cancer.

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