Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased?

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Abstract

***Objective*—To quantify the effect of selection of relatively healthy women in studies reporting reduced relative risk for cardiovascular disease in postmenopausal women taking hormone replacement therapy.**

***Design*—Review of the follow up studies reported in three recent meta-analyses to determine the effect of oestrogen therapy on both total cancer and cardiovascular disease. The same standard statistical methods as in the original analyses were used.**

***Main outcome measures*—Relative risks of total cancer and cardiovascular disease.**

***Results*—In most of the follow up studies the relative risk for total cancer was below 1. The studies that showed the largest reduction in cardiovascular disease also showed the largest reduction in cancer, indicating a healthy cohort effect. Although heterogeneity within the studies prevented pooling, the best estimate for the protective effect on total cancer was a relative risk of 0·83 among women taking oestrogen (95% confidence interval 0·71 to 0·96), while in the same studies the relative risk for cardiovascular disease was 0·57 (0·50 to 0·64).**

***Conclusions*—Unintended selection of relatively healthy women for oestrogen therapy may have influenced the reported beneficial effect of oestrogen therapy on cardiovascular disease. It is unclear how much of the cardioprotection is due to this selection. Universal preventive hormonal replacement therapy for postmenopausal women is unwarranted at present.**

Introduction

Recent meta-analyses show a 35-45% reduction in the risk of cardiovascular disease in women who have ever taken oestrogens.[1-3] This reduction in risk formed the basis of a policy statement by the American College of Physicians that stated that preventive hormone therapy should be considered in all postmenopausal women.[4] The meta-analyses are based on the results of observational studies, however, and can be influenced by unintended selection of relatively healthy women for oestrogen therapy.[5-8] Different baseline characteristics exist in favour of women taking oestrogen replacement.[9-12] Although meta-analysts acknowledge this form of selection bias, a quantitative appraisal of the problem has not been done. Selection of healthy women may be substantiated by showing a beneficial effect for a disease that is unlikely to be influenced by oestrogen—for example, no beneficial effect on total cancer would be expected from unopposed oestrogen in postmenopausal women. We therefore compared the relative risks for total cancer with the relative risks for cardiovascular disease in all follow up studies included in the recent meta-analyses.[13-30]

Methods

We used data from the original paper or reported in the associated literature on the same cohort. If insufficient data were reported we contacted the authors for information.[19 26-30] We calculated relative risks for total cancer and cardiovascular disease. We tested for homogeneity between the studies—that is, for the hypothesis that the difference between the estimated risks was due to random error around a true relative risk[31]—by using the sum of the squares of the differences between the estimated treatment effect and the estimated mean, weighted by the inverse squared standard errors. In a homogeneous subset of studies pooled estimates and 95% confidence intervals were obtained by precision weighting.[31]

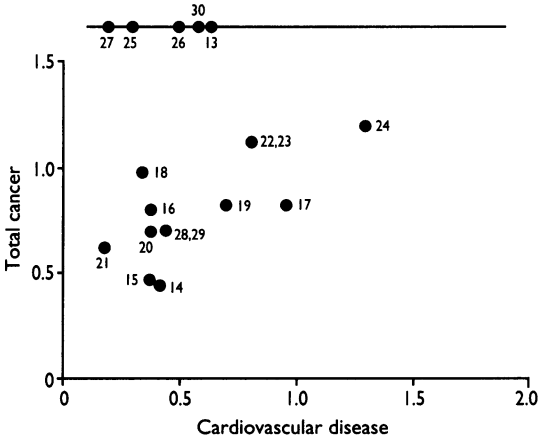
Results

The figure compares the relative risks for cardiovascular and total cancer within each study. In most studies the relative risk for total cancer was below unity, indicating protection. Moreover, the studies which showed the largest reduction in cardiovascular disease also showed the largest reduction in cancer.

The homogeneity test statistic was highly significant for both cardiovascular disease and total cancer ($P < 0.001$). This indicates that the studies do not estimate the same underlying relative risk and we therefore could not calculate precision weighted pooled estimates. When we restricted the analysis to the cohort studies that had been selected for reasons of methodological quality in the recent review by Grady *et al*,[3] there was less heterogeneity. In this subset[15 17 19 24 28 29] the precision weighted relative risk for cardiovascular disease became 0·57 (95% confidence interval 0·50 to 0·64) and the relative risk for total cancer was 0·83 (95% confidence interval 0·71 to 0·96). From the original estimate of 1·94 in the Framingham cohort,[29] the pooled relative risk for cardiovascular disease in this subset became 0·84 (95% confidence interval 0·72 to 0·96). The data provide us with a best overall estimate of the "protective" effect of oestrogen use on total cancer of almost 20%.

Discussion

We found that the relative risks for cardiovascular disease and total cancer were related within the studies.



Scatter plot of relative risks for cardiovascular disease and total cancer in women taking hormonal replacement therapy compared with those not taking it. Markers on line at top represent relative risks for cardiovascular disease in studies without data on cancer. Studies are identified by their numbers in reference list

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Clinical implications

- Hormone replacement therapy has been recommended for all postmenopausal women to prevent cardiovascular disease
- This recommendation is based on meta-analyses of observational studies
- Further analysis of the results from these observational studies also showed a reduced risk of cancer in women taking hormone replacement therapy
- As oestrogen increases the risk of or has no effect on cancer, the results suggest a healthy cohort bias
- Current evidence is insufficient to justify giving hormone replacement therapy to all postmenopausal women

This finding agrees with the hypothesis that there is unintended selection of healthy women for oestrogen therapy. The beneficial effect of oestrogen on total cancer is unlikely to be real because female reproductive cancers are, if anything, increased by oestrogens,[32 33] and for all other cancers no effect is known at present.

Apparently, women who take oestrogen replacement therapy enjoy a "healthy cohort effect." Firstly, there is self selection of women, as shown by their higher social class and social mobility.[32] Social class is inversely associated with mortality from several diseases including cardiovascular disease and cancer.[34-36] Secondly, there was selection of relatively healthy women by doctors who were reluctant to prescribe oestrogens to women with coronary risk factors 10 years ago. At that time oestrogen was contraindicated in these women because of earlier findings of raised risks of thrombosis and myocardial infarction in young women taking oral contraceptives and in older men treated with oestrogens.[37 38]

In most of the cohorts the relative risk for cardiovascular disease was lower than the relative risk for cancer. This raises the question whether we should simply subtract 20% from the 35-45% reduction in cardiovascular disease to arrive at a more appropriate estimate. However, the impact of the healthy cohort effect may be greater than 20%. In general the healthy cohort effect is stronger for cardiovascular disease than for cancer.[39-41] Most people who eventually develop cardiovascular disease show symptoms or primary risk factors a long time before and are therefore less likely to be included in a study cohort. By contrast, in cancer the first signs and symptoms are often those which lead to diagnosis of the disease.[40 41]

Our analysis strengthens the hypothesis that there is prominent selection for health among postmenopausal women taking oestrogen replacement therapy. This warrants a conservative estimation of the effect of oestrogen replacement therapy on cardiovascular disease. At a minimum the benefit of oestrogens will be smaller than suggested by the pooled estimates of the meta-analyses. Until the problem of selection for health is solved by a large randomised controlled trial or by studies that specifically address the problem of the healthy cohort effect, it seems premature to advocate hormone replacement therapy in postmenopausal women to prevent cardiovascular disease.

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