

References

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JOURNAL REVIEW

Oral contraceptive use and cancer. findings in a large cohort study, 1968-2004. Vessey M, Painter R. *J Cancer* 2006; **95**: 385-389

Following recent reports from the International Agency for Research on Cancer (IARC), concerns have been raised regarding the possible increased risk of various cancers relating to usage of the oral contraceptive (OC) pill. This large cohort study, leading on from previous reports from the Oxford Family Planning Association (FPA), set out to truly answer this question. Particular attention was focused on breast, cervical, uterine body and ovarian cancers and the potential beneficial effects on the latter two.

The study recruited and annually followed up women who attended UK family planning clinics from 1968 to 1974. The women were all married, white and aged 25-39 years. Most other confounding factors were well accounted for in the analysis. The study recruited 17 032 women, which totalled 540 000 woman-years. Annual follow-up was conducted until the age of 45 years with only a 0.4% annual loss rate to follow-up. The researchers analysed the effect of both the duration and interval since cessation of usage of the OC. The relative rate (RR) of non-gynaecological cancers was not affected by either of these factors and no correlation was shown. Of particular note is the nil effect seen on breast cancer and slightly protective effect some 20 years after cessation. The RR of cervical cancers was strongly influenced by duration of usage, with the RR varying from 2.9 after 4 years' usage to 6.1 after 8 years. A profound lingering effect of the OC on cervical cancer was also seen with a RR of 5.2 seen at 4 years after cessation and still 4.6 after 8 years. A strongly protective effect of the OC was shown for both uterine body and ovarian cancers. This was seen with uterine body cancer regardless of the length of time the OC was taken whereas such an effect on ovarian cancer was only evident after 4 years of therapy. The protective effect also persisted well beyond cessation of treatment, with RR of only 0.5 (uterine) and 0.6 (ovarian) seen 20 years after cessation.

This study looked at OC products containing 50 µg estrogen, which is relatively high for today's market. Therefore some effects seen here may not be as marked today. Naturally this study only deals with a streamed, predominantly Social Class I, health-seeking population but the use of RR instead of incidence does, I think, go a long way towards counteracting these and many confounders. When data were pooled on the three gynaecological cancers the RR in non-users versus users of the OC were 0.57 and 0.37. In essence this study clearly shows the harmful effects of OC usage on the RR of cervical cancer but that this is outweighed by the protection offered from uterine body and ovarian cancers.

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Specialist contraceptive counselling and provision after termination of pregnancy improves uptake of long-acting methods but does not prevent repeat abortion: a randomized trial. Schunmann C, Glasier A. *Hum Reprod* 2006; **21**: 2296-2303

This is an interesting and well-conducted randomised controlled trial powered to show a difference in uptake of post-termination contraception. Unfortunately only 53% of all eligible women were randomised and follow-up data were only available for 60% (control) and 63% (intervention) of the study participants.

The intervention, comprising a detailed interview/contraceptive counselling prior to or immediately after termination of pregnancy (TOP) and supply of contraception prior to discharge after TOP, led to increased uptake of contraception in the intervention group (271/316) compared to standard care (115/297, $p < 0.001$). This was particularly the case for uptake of long-acting contraception (141 in intervention vs 78 in control group, $p < 0.001$). However, at 4-month follow-up there was no longer a difference in overall use of or continuation of contraception nor was there any difference between the groups undergoing repeat abortion in the same hospital within the 2-year study period (14.6% vs 10%, $p = 0.267$).

Changing contraceptive behaviour seems to need more than a single intervention and easy access to first supply of contraception even if using long-acting methods.

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Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al.; Raloxifene Use for The Heart (RUTH) Trial Investigators. *N Engl J Med* 2006; **355**: 125-137

The Raloxifene Use for the Heart (RUTH) trial was initiated in 1998. This was at a time when observational studies suggested a reduced incidence of coronary heart disease (CHD) in postmenopausal women receiving estrogen therapy. This was further supported by the favourable effects of selective estrogen-receptor modulators (SERMs) on serum lipid profiles. Initially the trial was designed to assess the effect of 60 mg raloxifene on coronary events in women with already existing CHD or multiple risk factors.

A total of 10 101 postmenopausal women (mean age, 67.5 years) participated in this international, multicentre, randomised, double-blind, placebo-controlled trial. The median follow-up was 5.6 years. There were two primary outcomes in comparison to placebo: first, the incidence of coronary events (death from

coronary cause, non-fatal myocardial infarction or hospitalisation for acute coronary syndrome) and second, the occurrence of invasive breast cancer.

Raloxifene is a non-steroidal SERM with estrogen-agonistic properties in the bone and estrogen-antagonistic properties in the endometrium and breast. Previous evidence from the MORE trial in postmenopausal women with osteoporosis demonstrated a reduction in the risk of invasive breast cancer and no increase in endometrial pathology.¹ Additionally, raloxifene increased bone density in the spine and femoral neck with a reduction of vertebral but not hip fractures.² This had to be balanced against the increased risk of VTE.

The primary outcomes of the RUTH trial were as follows. Women receiving raloxifene had no increase in death from coronary causes, non-fatal myocardial infarction or hospitalisation for acute coronary syndrome in comparison to women receiving placebo. Raloxifene did reduce significantly the incidence of invasive breast cancer – primarily estrogen-receptor-positive invasive breast cancer – by 55%. Additionally, there was a significant risk reduction of clinical vertebral fractures by 35% but no reduction in non-vertebral fractures. These benefits have to be reviewed in the light of an increased risk of VTE (44%) and fatal stroke (49%). Other adverse events more commonly observed in the raloxifene group included hot flushes, peripheral oedema, gallbladder disease and leg cramps.

In summary, the RUTH trial confirms the benefits of SERMs in the reduction of invasive breast cancer and vertebral fracture. Raloxifene, in comparison to tamoxifen, does not increase endometrial pathology (confirmed in the MORE trial). Unfortunately these benefits have to be balanced against the increased risk of VTE and fatal stroke. Contrary to the initial trial design, a reduction in coronary events was not observed and therefore a cardio-protective effect cannot be assumed. Finally, the RUTH trial in comparison to the Women's Health Initiative trial did not include a 'global index'; the risks and benefits of SERM therapy should therefore be tailored to the individual needs of postmenopausal women.

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