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A Commentary on a recent update of the ovarian cancer risk attributable to menopausal hormone therapy

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ABSTRACT

The incidence of ovarian cancer is tenfold lower than that of breast cancer. The goal of the recently published meta-analysis by Beral and colleagues, using 'individual participant datasets from 52 epidemiological studies', was to provide an updated assessment of the effect of menopausal hormone therapy (MHT) on ovarian cancer risk. The relative risk generated from the cited prospective studies was significantly increased but the relative risk from the retrospective studies was not. This is quite unusual since retrospective studies usually display higher levels of relative risk. No further increase was observed with increasing duration. Moreover, a number of the studies could not be adjusted for important ovarian cancer risk factors. From the meta-analysis, it can be calculated that the absolute excess risk of 5 years of MHT for a 50-year-old UK woman is 1 in 10 000 per year, indicating a very low risk. We conclude that this meta-analysis mostly reflects the previously published data from the Million Women Study, from which the majority of this new publication is derived.

A recent paper in *The Lancet*[1] reports an increased risk of ovarian cancer in women using menopausal hormone therapy (MHT). It is a meta-analysis of 52 epidemiological studies, in which the analysis was separated into prospective and retrospective studies. Altogether, there were 21 488 cases and 63 846 controls; of these, 12 110 cases came from the prospective studies among which 6601 were observed in women who had used MHT for a median duration of 6 years.

Analysis of the global risk for ever-users compared to non-users (see Appendix and text) yielded a relative risk (RR) of 1.20 (95% confidence interval (CI) 1.13–1.28) in the *prospective* studies, 1.02 (95% CI 0.93–1.11) in the *retrospective* studies and 1.14 (95% CI 1.09–1.20) in all studies.

The first figure in the meta-analysis showed results specifically from prospective studies and reported an increased RR of 1.43 (95% CI 1.31–1.49) for a duration of MHT use less than 5 years and 1.41 (95% CI 1.34–1.49) for more than 5 years of use. The risk was non-significant after stopping MHT when MHT was taken for less than 5 years and remained increased at 1.29 (95% CI 1.11–1.49) for more than 5 years' use. After 5 years since last use, no increased risk was seen. By contrast, the retrospective studies ($n = 32$), either from Europe, the USA or pooled, did not show any increase in the risk, with a RR of 1.04 (95% CI 0.93–1.16). It is quite unusual to see a lower risk from retrospective case–control studies which usually amplify the risk.

Furthermore, as reported here, the risk does not increase with duration of use. Again, it is quite unusual that duration does not increase the risk if the factor is causal. This suggests that diagnostic bias may have occurred.

The interpretation proposed by the authors to explain the difference between prospective and retrospective studies is that the retrospective studies concerned earlier times when MHT use was less prevalent than more recently: the mean year of diagnosis was 1994, 29% of the women used MHT and the mean duration of use was 4 years, whereas, in prospective studies, the mean year of diagnosis was 2000, 55% of the women were users and the median duration of use was 6 years. This argument is not really convincing since about of 30% of users correspond more to the reality of the proportion of women using MHT, as for example in the EPIC study[2]. Furthermore, the earlier years corresponded to higher doses of MHT.

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COMMENTARY

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This paper tries to analyze the level of risk of ovarian cancer during or after MHT use. This exemplifies the limits of meta-analysis. Certainly, the justification is that ovarian cancer incidence is low. The randomized Women's Health Initiative failed to see any significant effect, perhaps due to lack of adequate power, and perhaps because of the availability of correct adjustment.

Several major flaws in this meta-analysis should be discussed: relative risks were claimed to be adjusted for body mass index, age at menopause, oral contraceptive use and parity. This is not true for all the studies; in some studies, not all these variables were available. Indeed, in meta-analysis, the results mostly reflect the more powerful studies. Here, two prospective studies weighted heavily: the Million Women Study (MWS)[3] and the Danish Sex Hormones Register Study (DaHoRS)[4], respectively accounting for 1500 cases and 2500 controls and 600 cases and 1384 controls, i.e. 2100 of the total of 2751 (76%) cases and 3884 of the total number of 5429 (71.5%) controls for the prospective studies. The reference used in the meta-analysis for the DaHoRS was published in 2009; there is a more recent publication from the same group: *Am J Epidemiol* 2012;175:1234–42. Why were the more recent data not used? However, in the DaHoRS, the information on oral contraceptives, body mass index and age at menopause was lacking as it is a study based on data from registers.

Thus, the results published here represent mostly the MWS data and the adjustments were only partially possible. It is indeed quite difficult to pool studies where different variables are not all available and then the adjustments cannot be done. The EPIC study, another important (but less powered) observational study, showed an increased risk of ovarian cancer which increased with duration of MHT (significant after 5 years) but, despite having most of the variables for adjustment, still the familial history of breast and ovarian cancer was lacking[2].

Another compelling finding is that estrogen-only therapy (ET) and combined estrogen–progestin therapy (EPT) were associated with equivalent risks. It is surprising since most of the studies reported a higher risk associated with ET (MWS, EPIC, a previous meta-analysis combining 14 studies[5]). The higher risk of ovarian cancer associated with ET could arguably be because ET is mostly prescribed in hysterectomized women, where the occurrence of ovarian cancer is due not to MHT but to causal diseases promoting pelvic disorders and being the indication for hysterectomy. The MWS showed a higher risk with estrogen-only therapy.

In the Appendix, some additional interesting data are available. Tables show the relative risks of ovarian cancer in current users versus never-users according to risk factors such as body mass index, oral contraceptive use, parity, smoking, alcohol, age at menarche, a first-degree relative with an ovarian cancer and hysterectomy. These subanalyses were made where the information was available in prospective studies and concerned 2151 cases and 7436 controls among the population of recent/current users versus controls. This highlights that adjustments could be made only in a subpopulation. The risks were not altered by any of these factors, which is quite unexpected.

A major factor decreasing the relative risk is oral contraceptive use. When the MWS was published, we wrote a letter, published in *The Lancet*[6], to ask the authors to analyze their results according to the use of oral contraceptives. Their comments were: 'Women's previous use of oral contraceptives does not seem to modify the effect of HRT on ovarian cancer – our published results showed no significant difference in the effect of HRT between women who had and had not used oral contraceptives. Anne Gompel and Genevieve Plu-Bureau asked for further subdivisions of the data, by duration of use or time since last use of oral contraceptives. The relative risks for current versus never-use of HRT are 1.32 (95% CI 1.08–1.62) among women who used oral contraceptives for less than 5 years, 1.02 (95% CI 0.77–1.35) among those who used them for 5–9 years, 1.12 (95% CI 0.83–1.51) among those who used them for 10 years or more, 1.14 (95% CI 0.81–1.59) among those whose last use was less than 20 years previously, and 1.20 (95% CI 1.02–1.41) among those whose last use was longer ago than 20 years. None of the differences between the subgroups are significant.'[7].

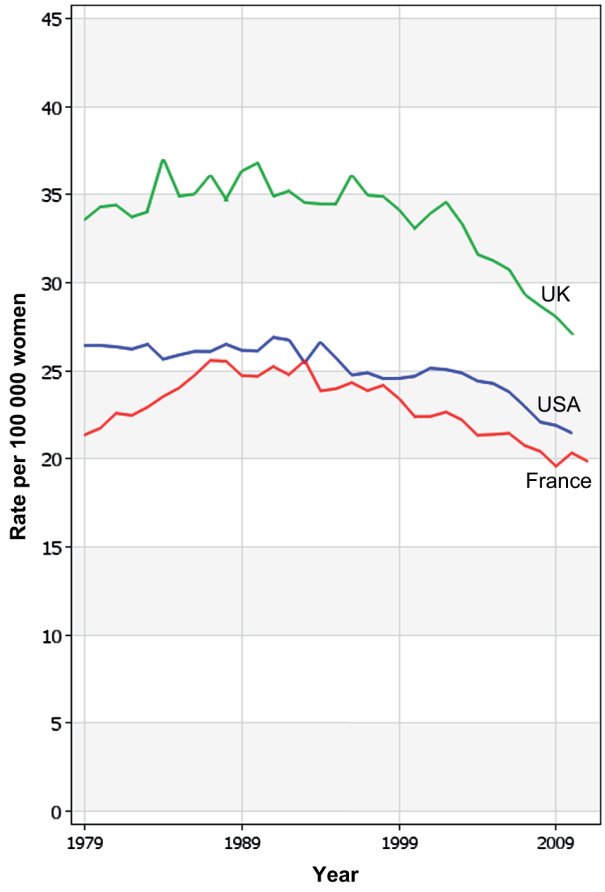

Figure 1 Mortality from ovarian cancer, age-standardized rate (world) for women aged 50–85 years in the USA, the UK and France in the last 30 years, from reference 8

We can, however, note that the relative risk in women using oral contraceptives for more than 10 years is lower than for women who used oral contraceptives briefly, and higher in women who stopped oral contraceptives more than 20 years ago.

The authors of *The Lancet* paper calculate that, in the UK, combining all women aged 50–64 years, there will be an additional one case per 1000 women per 5 years of MHT use. It is important to distinguish this figure from the absolute risk of using MHT for an individual woman. This risk is lower for women aged 60–64 years than those 50–54 years old. For the latter group, it can be calculated that the absolute risk is about 1 per 10 000 women per year of use, with a base rate of 1.2 per 1000 per 5 years and an absolute excess of 0.55 per 1000 per 5 years.

And last but not least, the biological plausibility for an increasing risk of serous and endometrioid tumors is more or less lacking. It is most surprising that a major protective factor decreasing ovarian cancer incidence is oral contraceptive use. MHT contains hormones as do oral contraceptives. There are very few data on the potential mechanisms for estrogens and progestins to increase the risk. It is usually thought that estrogens induce the proliferation of epithelial ovarian cells and progesterone could be pro-apoptotic. In fact, there are two types of serous ovarian cancer with different prognosis, different origin and thus mechanisms. Why is the effect of MHT on type I and type II not considered separately? It is also very likely that the transduction pathways involved in the endometrioid and serous cancers are not the same. How is it possible to imagine that hormones can drive tumors of such different differentiation in the same way? More information is definitely needed to specifically understand the potential roles of estrogens and progestins in the course of the ovarian cancers.

We reproduce in Figure 1 the rates for ovarian cancer deaths obtained from the World Health Organization data according to years and in women over 50 years old[8]. There has been a regular decrease in the rates since the 1990s. A more important decrease was perhaps seen in the USA and the UK since 2006 but not in France, where the decrease is more or less linear, suggesting that the role of MHT remains not fully determined.

CONCLUSIONS

This meta-analysis appears to give a strong confirmation of an increased risk of ovarian cancer, especially serous and endometrioid tumors, and this risk is equivalent with ET and EPT. Unfortunately this relies on an analysis containing possible flaws and reflects mostly the previous data from the MWS. It does not contribute to a more specific evaluation of the level of increase in the risk of ovarian cancer and MHT use. Nevertheless, even accepting the risk as reported in this study, its impact on public health remains very low.

Conflict of interest Anne Gompel: Financial or business/organization interests: International Menopause Society, European Society of Endocrinology, *Climacteric* (journal), The Endocrine Society. Financial interest or leadership position: European Society for Contraception, GEMVI, Société Française de Sénologie et Pathologie Mammaire. Henry Burger reports no conflict of interest.

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