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An analysis of ovarian cancer in the Million Women Study

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Abstract
In a reanalysis of the Million Women Study (MWS), their authors concluded that prolonged use of hormone replacement therapy (HRT) in postmenopausal women increases the risk of ovarian cancer. Although statistically significant their results are clinically irrelevant, since the attributable risk over 5 years is only 4 per 10 000 HRT users, a figure that is not confirmed by other large studies. This risk is much lower than those associated with obesity, lack of physical exercise, smoking and nulliparity, all of which are preventable. Therefore HRT should continue to be prescribed for symptom relief and improvement of quality of life because the benefits far outweigh the very low potential risks.

Keywords: *Ovarian cancer, HRT, MWS*

The Million Women Study (MWS) has extracted from its files some important data about ovarian cancer in postmenopausal women who use hormone replacement therapy (HRT) [1]. In summary, it was concluded that the 'crude incidence and mortality rates for ovarian cancer in the study population as a whole were 2.2 and 1.3, respectively, for 1000 women over 5 years. In never users of HRT the standardized rates were 2.2 (2.1–2.3) and 1.3 (1.2–1.4) respectively, and in current users the corresponding rates were 2.6 (2.4–2.9) and 1.6 (1.4–1.8), respectively'. This means that the *attributable risk* of ovarian cancer in postmenopausal HRT users is 0.4 and 0.3, respectively, per 1000 women over 5 years, or that 'over a 5 year period use of HRT resulted in about one extra case of ovarian cancer in every 2500 users and one extra death from malignancy in every 3300 users . . . The risk of developing ovarian cancer increased with increased duration of HRT use (test for trend, $p = 0.04$) and the relative risk was 1.31 (1.12–1.53) for the 10 or more years of use'. This is a much clearer way to explain the meaning of the reported 20% increase in risk, which is obviously an expression of the relative risk rather than the absolute risk.

This study is very difficult to interpret and extrapolate into clinical practice, and may lead to misleading conclusions.

The process of carcinogenesis takes time to express itself as a tumor and once it starts it keeps going on and on, either independently or under the influence of growth factors. 'Women who developed the cancer were diagnosed on average 2.4 years after the date that use of HRT was last reported' and 'women who had stopped taking HRT had a similar risk of ovarian cancer to that in women who had never used HRT'. Thus the MWS concluded that 'the use of HRT by postmenopausal women increases the risk of ovarian cancer and that this excess risk disappears shortly after use ceases'.

This is highly suggestive of occult ovarian cancers, with estrogen and progestogen receptors, that may have grown under the stimulation of these steroids and that regressed upon cessation of this stimulation. Just like in the breast, where dormant cancer cells may exist and be stimulated later [2], the same may occur in the ovary. With thousands of mitoses going on every day it is inconceivable that some of them are not abnormal and result in a mutant cancer cell. The immunologic defenses of the body may keep it in a

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dormant state. A decrease in the immune defense or the appearance of new growth factors may then contribute to its resuscitation as an active cancer cell that would, with time, manifest itself as a growing tumor [3].

The ovary is both an endocrine organ and an end organ. The surface epithelium of the ovary contains both types of estrogen receptor (ERα and ERβ), growth factors and cytokines, which are strong candidates to regulate the ovarian transformation and progression of ovarian cancers [4]. In sheep, the expression of estrogen (ERβ, ERα), androgen and progesterone receptors was also observed in the surface epithelium and ovarian stroma of the fetal, neonatal and adult ovary [5]. In cows the cells of the surface epithelium of the ovary had a moderate score for ERβ mRNA, whereas cells of the tunica albuginea and deep stroma showed high ERβ mRNA scores [6]. Recently specific tumor vascular proteins have been identified in ovarian cancers [7] which make it possible for estrogens to stimulate angiogenesis in an occult silent tumor. A similar situation is known to occur with breast cancer since about 20% of women, without any previous hormonal treatment, were found to have occult asymptomatic cancers in autopsy material [8].

'The risk of both types of cancers (ovary and breast) increases with increasing duration of use among current users but returns to that observed in never-users soon after use ceases ... Compared with never users the risk of ovarian cancer is significantly increased in current users 1.2 (1.09–1.3), $p = 0.0002$. Ever users had a slightly increased risk of ovarian cancer (relative risk 1.11 (95% CI 1.02–1.21), $p = 0.002$)'.

These findings are again suggestive of the presence of occult asymptomatic ovarian cancers at the time of institution of HRT. Of the 'current users who developed ovarian cancer, the estimated duration of use of HRT at the time of diagnosis was 7.7 years, overall ... Past users who developed ovarian cancer had ceased use of HRT an average of 5.6 (5.0–4.3) years before they were diagnosed with malignancy'. However, the relative risks 'were close to 1.0 for women who had ceased use of HRT less than 5 years previously (1.01 (0.87–1.18))'.

To cut a long story short, the *attributable risk* of incidence and mortality due to ovarian cancer in postmenopausal women under HRT is very small, i.e. 4 and 3 per 10 000 women over 5 years, respectively. It is noteworthy that neither the Women's Health Initiative (WHI) [9] nor the Nurse's Health Study (NHS) including over 120 000 female nurses [10] reported an increase in overall mortality (certainly also including ovarian cancer). The WHI lasted 5.6 years and the NHS has been running since 1976. Thus one would expect to see in the latter an increased incidence of ovarian cancer, which is not the case. The MWS detected a rise in the incidence of ovarian cancer '2.4 years after the date that use of HRT was last reported' and that 'the estimated use of HRT at the time of diagnosis was 7.7 years overall', which is in contradiction with the National Institutes of Health–AARP Diet and Health Study cohort, including 97 638 women aged 50–71 years at baseline [11], which found that 'the use of unopposed estrogen for fewer than 10 years was not associated with ovarian cancer'.

Then, is this relevant compared with other risks for ovarian cancer? Here are some examples.

(1) 'Among premenopausal women (<50 y old), those classified as obese had a significantly increased risk (adjusted OR = 2.19; 95% CI 1.19–4.04) compared with women classified as normal/underweight. These findings suggest a potential influence of menopausal status on the total endogenous hormonal environment, including estrogens, androgens, and insulin-like growth factors, when considering the association between body size and ovarian cancer risk' [12].

(2) 'A trend of increasing risk of ovarian cancer was seen with increasing age at first birth. The adjusted RR was 0.69 (95% CI = 0.52–0.90) for women who bore two children, and 0.30 (95% CI = 0.21–0.42) for women with three or more births, respectively, when compared with women who had given birth to only one child. There was a significant decreasing trend in the adjusted RR of ovarian cancer with increasing parity. This study provides evidence that parity may confer a protective effect on the risk of ovarian cancer' [13].

(3) 'The pooled effect estimate for adult obesity was 1.3 (95% CI 1.1–1.5) with a smaller increased risk for overweight (OR 1.2; 95% CI 1.0–1.3). The pooled OR was stronger among case control studies (OR = 1.5) than cohort studies (OR = 1.1)' [14].

(4) 'After stratification by menopausal status, BMI showed no significant association to ovarian cancer risk among postmenopausal women (≥ 50 y old). However, among premenopausal women (<50 y old), those classified as obese had a significantly increased risk (adjusted OR = 2.19; 95% CI 1.19–4.04) compared with women classified as normal/underweight' [12].

(5) 'Meta-analysis suggests that current smoking doubles a woman's risk of developing mucinous ovarian cancer. Stopping smoking returns the risk to normal in the long term. Smoking may thus be one of the few modifiable factors offering potential for primary prevention of mucinous ovarian cancer' [15].

(6) 'Regular drinking of beer (1 drink/day or more) during ages 20–30 (OR 1.55, 95% CI 1.07–2.26), though not liquor (OR 1.35, 95% CI 0.86–2.11) or wine (OR 0.99, 95% CI 0.49–2.00), was associated with a statistically significant increase in risk of invasive tumors, whereas no significant relationships were observed for recent drinking, regardless of alcohol type. The elevated risk for early adult regular drinking was confined to serous invasive tumors (OR 1.52, 95% CI 1.01–2.30)' [16].

(7) 'The risk among women in the top tenth, relative to women in the lowest fourth, of the distribution of body weight at age 18 years was 1.5 (95% confidence interval, 1.0–2.2); at age 30, 1.9 (1.2–2.9); and 5 years before the reference date, it was 2.1 (1.4–3.3). While our results did not substantiate risk elevations reported in previous studies among subsets of women (e.g. with particular histologic tumor subtypes or according to past oral contraceptive use), we noted a particularly increased risk among women who reported 10 or more pounds gained during their first year of oral contraceptive use. Our findings suggest that risk of epithelial ovarian cancer may be most closely linked with body weight in the relatively recent past (but before the time in which the disease may manifest as weight loss) among women who develop this disease during the years before or shortly after menopause' [17].

(8) 'Adjusted OR for recent body mass index {BMI} quartile 4 compared with quartile 1 for nulliparous women was 2.53 (95% confidence interval [CI]: 1.39, 4.61) compared with 0.96 (95% CI: 0.70, 1.31) for parous women. Additionally, adult weight gain was significant only for nulliparous women. Adjusted OR for weight change (recent to age 18) quartile 4 compared with quartile 1 for nulliparous women was 3.73 (95% CI: 1.88, 7.42) versus 1.09 (95% CI: 0.78, 1.51) for parous women . . . BMI and weight in women's adult lifetime may be positively associated with ovarian cancer risk. Observations were most apparent for nulliparous women, possibly reflecting an interaction between local inflammation caused by incessant ovulation and increased estrogen exposure on ovarian epithelium' [18].

(9) 'Results indicate that decreased risk of ovarian cancer was associated with being a nonsmoker exposed to ETS (adjusted odds ratio [aOR] 0.68, 95% confidence interval [CI] 0.46–0.99), a former smoker (aOR 0.76, 95% CI 0.53–1.10), or a current smoker (aOR 0.53, 95% CI 0.32–0.88)' [19].

(10) 'A prolonged duration of sedentary behavior was associated with an increased risk (for ≥ 6 vs. < 3 hours per day: hazard rate ratio $= 1.55$, 95% confidence interval: 1.08, 2.22; p (trend) $=$ 0.01). Results from this study suggest that high levels of sedentary behavior may increase the risk of ovarian cancer, but they do not support a major impact of light and moderate physical activity on ovarian cancer risk' [20].

(11) 'We observed an increased risk of ovarian cancer among women who, during the 5-year study period, did not have a medical visit (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.5–5.0) or pelvic examination (OR 3.9, 95% CI 2.2–6.9) or who had no regular health care provider (OR 2.7, 95% CI 1.3–5.7). This increase in risk was most pronounced among women who were postmenopausal (no medical visit, OR 7.7, 95% CI 2.6–23.0; no pelvic examination, OR 3.3, 95% CI 1.7–6.0; no health care provider, OR 12.5, 95% CI 2.7–57.5)' [21].

Large epidemiological studies are extremely important to suggest or to prove cause-and-effect associations. Nevertheless, the interpretation of these results requires careful attention since none of them is devoid of biases that may lead to misleading interpretations or conclusions.

When referring to risks it is always a serious error to point out only the relative risks in users without adding the *attributable risks* and the numbers needed to harm, which are much more valuable indicators both for medical professionals and the users of a particular therapy. The media wrongly exposes the relative risks in headlines and this contributes to a major disorientation that takes years to correct into the right perspective.

Therefore, the conclusions of the MWS concerning ovarian cancer in postmenopausal HRT users, although statistically significant, are *clinically irrelevant* for clinical practice when balancing benefits versus risks.

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