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## HORMONE REPLACEMENT THERAPY AND RISK OF ENDOMETRIAL CANCER

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An association of endometrial cancer with hormone replacement therapy (HRT) was suggested on the basis of a substantial rise in the incidence of the disease observed in the United States in the early 1970s, following widespread HRT use. Epidemiological evidence now confirms the association between estrogen use and endometrial cancer risk, and the persistence of elevated risk several years after cessation of use<sup>1-4</sup>. The risk is about 2-3 times

greater in ever than in never estrogen users, since the summary relative risk (RR) from a meta-analysis of published studies was 2.3 (95% CI 2.1-2.5)<sup>5</sup>; the RR were similar for cohort (RR 1.7) and case-control studies using hospital (OR 2.2) or population (OR 2.4) controls. The risk was related to duration of use: the RR was 1.4 for use <1 year, 2.8 for 1 to 5 years, 5.9 for 5-9 years and 9.5 (95% CI 7.4-12.3) for ≥10 years<sup>5</sup>. The risk was also inversely related with time since last use<sup>5</sup>, suggesting that estrogens have a late-stage effect in endometrial carcinogenesis<sup>6,7</sup>.

Estrogen-associated risks for endometrial cancer tend to be higher in leaner than overweight women, who have higher endogenous estrogen levels and availability. The combined effect of exogenous and endogenous estrogens is additive rather than multiplicative, suggesting that exogenous estrogens and obesity act through similar biological mechanisms on the risk of the disease<sup>8</sup>. Some studies suggested a greater excess risk among smokers<sup>9,10</sup> (who tend to have lower estrogen availability), and a lower excess risk among ex-users of combined oral contraceptives<sup>10,11</sup>.

Data on type of estrogen, dose, bioavailability, regimen, or duration of use are inconsistent; overall these variables appear not clearly associated, although users of high-dose preparations tend to have a higher risk<sup>1,4</sup>. In the meta-analysis by Grady *et al.*<sup>5</sup>, the RR was 3.9 (95% CI 1.6-9.6) for users of 0.3 mg conjugated estrogens, 3.4 (95% CI 2.0-5.6) for users of 0.625 mg, and 5.8 (95% CI 4.5-7.3) for users of ≥1.25 mg. As for the type of compound used, the RR was 2.5 for users of conjugated estrogens and 1.3 for users of synthetic estrogens<sup>5</sup>. The cyclic addition of progestins to estrogens for at least 7 days/month protects against endometrial hyperplasia (a supposed precursor of endometrial cancer)<sup>1</sup>. The RR from a meta-analysis of endometrial cancer in women using cyclic combined therapy was 0.8 (95% CI 0.6-2.2)<sup>5</sup>. The number of days/month of progestin addition is an important determinant of risk. In a study from Washington State the RR was reduced from 2.4 to 1.1 for addition of progestins for ≥10 days/month<sup>12</sup>, and in another from California<sup>13</sup>, the RR for ever users was 3.1 for <10 days/month of added progestins and 1.3 (95% CI 0.8-2.2) for 10-21 days. Another study from Los Angeles County<sup>14</sup> showed RRs for 5 year use of 2.2 for unopposed oestrogen, 1.9 for estrogens plus progestins for <10 days/month, and 1.1 (95% CI 0.8-1.4) for progestins added for <10 days/month. A Swedish study of post-menopausal women confirmed a strong association of endometrial cancer with unopposed estrogen use (RR 6.2 for estradiol and 6.6 for conjugated estrogens for ≥5 year use), with a much weaker association for the combination of estrogens and progestins (RR 1.6, 95% CI 1.1-2.4), and an inverse association for continuous use of progestins (RR 0.2, 95% CI 0.1-0.8 for ≥5 year use)<sup>15</sup>. A record linkage study, conducted in Sweden on a cohort of 8,438 women at risk of endometrial cancer, found a RR of 4.2 for 6 years use of unopposed estrogens, and of 1.4 (95% CI 0.6-3.3) for combined estrogen and progestin therapy<sup>16</sup>. In a Canadian study the RR was 4.1 for use >5 years of unopposed HRT, and around 1.5 (borderline significance) for various types of combined therapies<sup>17</sup>. According to a nationwide cohort study from Finland, the long-cycle (3-months) HRT use was associated with a greater endometrial cancer risk (RR 2.0) compared to monthly cycle HRT (RR 1.3)<sup>18</sup>.

Thus, although the use of estrogens alone may increase endometrial cancer risk, several studies indicate that combined therapy is not related to a major excess of endometrial cancer, if progestins are given for >10 days/month<sup>19</sup>.

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## Cervical and endometrial cancer treatment

Chairmen: C Scarabelli, F Santi

### SURGICAL TREATMENT OF INVASIVE CERVICAL CANCER

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The Department of Obstetrics and Gynecology in Ljubljana has a long tradition in radical gynecological surgery. Due to Franc Novak's work in the early '50s, the percentage of ureterovaginal fistulas after Wertheim hysterectomy diminished from 10-12% all over the world to only 2% in Ljubljana, in spite of extensive radicality and preoperative irradiation<sup>1</sup>. Un-

fortunately, the indications for radical vaginal hysterectomy see Schauta over the last 20 years have been reduced, because in the past the main indication for the Schauta operation was microinvasive cervical cancer. Nowadays, with the introduction of laparoscopic lymphadenectomy, the Schauta operation may have a revival and new indications<sup>2</sup>. Regarding the surgical procedure there has been a significant reduction of radicality in the treatment of microinvasive cancer (stage Ia) after the year 1981, when a 'scoring' system of prognostic factors was introduced<sup>3</sup>. The evaluation of morphologic criteria is based upon type of cells, mitotic activity, type of invasion, lymphoplasmatic infiltration, lymphovascular space invasion and depth of invasion. Nowadays more than 60% of stage Ia cases can be successfully treated only with conization, which is confirmed with appropriate follow-up<sup>4</sup>. Wertheim procedure with pelvic lymphadenectomy is the treatment of choice in patients with localized disease: the surgery is performed in patients in good general condition, younger than 65-70 years and have stage Ib or IIa (early stage IIb only exceptionally). On the basis of our experiences and of those of others<sup>5</sup> it is nowadays possible to modify the radicality of parametrial excision and lymphadenectomy according to the tumor volume (old 'classical' Wertheim-Piver II or 'new' Wertheim-Meigs-Novak-Piver III), and thus avoid the long term postoperative urological complications. Our latest survival analysis of patients with stages Ib and IIa cervical cancer, operated at our Department in the period 1988-95 showed the 3-year survival rate to be 92.8% (269/290 patients) and the 5-year survival rate to be 90.0% (181/201 patients). The recurrences occur mainly within the first 3 years. Our data show that there is no significant difference in survival of squamous cell carcinoma (91%) and adenocarcinoma (83%) cases and that the worst prognostic factor (which correlates with the tumour volume) is lymph node involvement: 14% of patients had positive nodes and only a 75% survival rate compared with a 92.4% survival rate in the patients with negative nodes. Postoperative irradiation (rarely in combination with chemotherapy until now) was used in node positive or cases with deep cervical invasion; in these cases the survival was 80% compared with 96% in cases not irradiated postoperatively. In our experience only the 'new' Wertheim (Piver III) can lead to urological complications such as ureterovaginal fistulas and bladder dysfunction, mainly due to dissection of the anterior parametrium with subsequent extensive resection of the lateral parametrium. Of the 544 patients operated in the period 1988-98 major complications were rare: no case of primary mortality, 2% of pelvic infection and 1% of ureterovaginal fistulas. In conclusion we can affirm that most of microinvasive cases can be treated conservatively with conization, whereas radical hysterectomy is mandatory in younger patients with localized disease and in adenocarcinoma cases.

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