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IV.3 The Combined Effects of ERT, Obesity and Tamoxifen Therapy for Breast Cancer on Endometrial Cancer Risk

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TAMOXIFEN, WIDELY used to treat breast cancer, is currently under evaluation as a breast cancer prevention agent in clinical trials. Reports that tamoxifen induces endometrial cancer have raised concern among consumers and practitioners. No prior studies of tamoxifen's effects on endometrial cancer risk have examined the modifying effects of oestrogen replacement therapy (ERT) and obesity. We examined these effects in a matched case–control study of subsequent endometrial cancer following breast cancer conducted within four Surveillance Epidemiology and End Results (SEER) registries (Los Angeles, Iowa, Seattle, and Atlanta cases). The medical histories of 324 case-patients and 671 control-patients were established through the review of medical records and by interview. Tamoxifen use, ERT use and obesity were each statistically significant predictors of endometrial cancer risk. The effect of tamoxifen on endometrial cancer risk was duration related (trend $P=0.001$); relative to non-users, women with more than 5 years exposure to tamoxifen had 3.7-fold greater odds of developing endometrial cancer. Among women with prior ERT exposure, the trend in risk was more pronounced (trend $P<0.0001$) than it was for those with no prior use of ERT (trend $P=0.11$) and this difference was statistically significant (homogenecity $P=0.0001$). The risk of endometrial cancer associated with duration of tamoxifen use also varied by obesity status, with the trend in risk more pronounced among heavier women. Among women above the median body mass index of controls in the study, the odds of endometrial cancer was more than 5-fold greater if the woman had used tamoxifen for more than 5 years; among thinner women, the relative odds of endometrial cancer after more than 5 years of tamoxifen therapy was less than 2. Risk of endometrial cancer associated with tamoxifen therapy was most elevated among those women who previously took ERT and who had high body mass index when diagnosed with breast cancer. These results suggest that both exogenous and endogenous oestrogens substantially modify the effects of tamoxifen on endometrial cancer risk.

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IV.4 Iatrogenic Risks of Endometrial Carcinoma after Treatment for Breast Cancer in a Large French Case–Control Study

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In a case–control study, including 135 cases of endometrial carcinoma diagnosed after breast cancer and 467 controls, the relative risks for endometrial carcinoma were higher for women treated with

tamoxifen (4.9; $P=0.0001$) and those who undergone pelvic radiotherapy (7; 8; $P=0.0001$). After adjusting for confounding factors, a multivariate analysis has shown an increased risk of endometrial carcinoma for tamoxifen users, especially for treatment longer than 3 years and for pelvic radiotherapy. Patients treated with tamoxifen had more advanced tumours and lower survival rates than those who had not received tamoxifen. © **1998 Elsevier Science Ltd. All rights reserved.**

EVALUATE, WITHIN a large case–control study, the risk of endometrial carcinoma (EC) after tamoxifen (TAM) treatment but also other therapeutic modalities such as pelvic irradiation in breast cancer (BC) women. To study the pathological characteristics of EC after BC. To appreciate survival for these patients.

In a case–control study in 14 French hospitals, 135 cases of endometrial carcinoma (EC) after breast cancer (BC) were individually matched with 487 controls for age, year of diagnosis of breast cancer, hospital and survival time with intact uterus.

No difference was noted for BC between cases and controls for age, menopausal status or parity. At diagnosis of BC, more stage 3 and 4 were noted among cases (19.2 versus 8.2%: $P=0.002$). Axillary node involvement was more frequent among cases and reached significance for more then 3 N+ ($P<0.01$). No difference was noted between the two groups for surgical treatment or radiotherapy. According to staging, more cases received adjuvant chemotherapy, compared to controls (44.8 versus 31.8%, $P<0.01$). Tamoxifen (TAM) was taken by 91 cases and 191 controls ($P<0.001$) and pelvic radiotherapy (12–15 Gy) had been performed in 33 cases and 59 controls ($P<0.001$).

The crude relative risk (RR) of endometrial carcinoma was higher in women treated by TAM compared to untreated women (RR = 4.9, $P=0.0001$). During the study period, the median duration of treatment by TAM was longer for cases (50 m. versus 34 m.), leading to higher risk with longer duration of treatment, irrespective of the daily dose (trend per year: 1.5, $P=0.0001$). The RR of EC was higher with cumulative doses over 7.5 g and particularly for dosages greater than 30 g (trend per gram: 1.05; $P=0.0001$). Among other therapeutic modalities, an increased risk was also noted for pelvic radiotherapy (RR = 7.8, $P=0.0001$).

In a multivariate analysis including the therapeutic factors and controlling for potentially confounding factors (stage of BC, axillary nodal status, hormonal receptor status), the RR for EC was significantly increased in women treated with TAM (RR = 4.5, $P=0.0012$), duration of treatment of 3 years or more (RR = 3.9, $P=0.024$) and with pelvic radiotherapy (RR = 3.2, $P=0.012$).

The median interval between the two cancers was longer for tamoxifen treated women (62 m. versus 52 m. $P=0.056$). Frequency of gynaecological signs was similar at diagnosis of EC but more tumours were FIGO stage 2 and plus among the tamoxifen-treated women. Tumours were mainly differentiated adenocarcinomas. However, 6 mixed mullerian tumours were reported (all in the exposed group). The distribution of histological types was not significantly associated with tamoxifen nor with pelvic radiotherapy ($P=0.8$ and 0.9, respectively).

The median duration of follow-up after endometrial carcinoma was 41 months for tamoxifen-treated women and 84 months for untreated women. The overall survival rate after endometrial carcinoma was significantly longer for women who had not received tamoxifen than for those treated by tamoxifen alone or in combination with pelvic radiotherapy ($P=0.035$ and $P=0.0005$, respectively).

Prescription of tamoxifen in women with breast cancer should be associated with gynaecological surveillance, especially when the drug is given for more than 3 years or combined with pelvic radiotherapy. Methods of such a screening have to be evaluated.

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