A7. HORMONE REPLACEMENT THERAPY AND BREAST CANCER RISK. THE MILLION WOMEN STUDY[1]

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Background: Current use of hormone-replacement therapy (HRT) increases the incidence of breast cancer. The Million Women Study was set up to investigate the effects of specific types of HRT on incident and fatal breast cancer.

Methods: 1084110 United Kingdom (UK) women aged 50–64 years were recruited into the Million Women Study between 1996 and 2001. They provided information about their use of HRT and other personal details, and were followed up for cancer incidence and death.

Findings: Half of the women had used HRT; 9364 incident invasive breast cancers and 637 breast cancer deaths were registered after an average of 2.6 and 4.1 years of follow-up, respectively. Current users of HRT at recruitment were more likely than never users to develop breast cancer (adjusted Relative Risk 1.66 [95% Confidence Interval (CI) 1.58–1.75], $P < 0.0001$) and die from it (1.22 [1.00–1.48], $P = 0.05$). However, past users of HRT were not at an increased risk of incident or fatal disease (1.01 [0.94–1.09] and 1.05 [0.82–1.34], respectively). Incidence was significantly increased for current users of preparations containing oestrogen only (1.30 [1.21–1.40], $P < 0.0001$), oestrogen-progestagen (2.00 [1.88–2.12], $P < 0.0001$), and tibolone (1.45 [1.25–1.68], $P < 0.0001$), but the magnitude of the associated risk was substantially greater for oestrogen–progestagen than for other types of HRT ($P < 0.0001$). Results varied little between specific oestrogens and progestagens or their doses; or between continuous and sequential regimens. The Relative Risks were significantly increased separately for oral, transdermal, and implanted oestrogen-only formulations (1.32 [1.21–1.45]; 1.24 [1.11–1.39]; and 1.65 [1.26–2.16], respectively; all $P < 0.0001$). In current users of each type of HRT, the risk of breast cancer increased with increasing total duration of use. 10 years of ' use of HRT is estimated to result in five (95% CI 3–7) additional breast cancers per 1000 users of oestrogen-only preparations and 19 (15–23) additional cancers per 1000 users of oestrogen–progestagen combinations. Use of HRT by women aged 50–64 years in the UK over the past decade has resulted in an estimated 20 000 extra breast cancers, 15 000 associated with oestrogen-progestagen; the extra deaths cannot yet be reliably estimated.

Interpretation: Current use of HRT is associated with an increased risk of incident and fatal breast cancer; the effect is substantially greater for oestrogen-progestagen combinations than for other types of HRT.

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A8. PREGNANCY AND BREAST CANCER

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Pregnancy protects against breast cancer (BC). Early full-term pregnancy protects even better. Various hypotheses explain this: terminal differentiation of end buds (Russo), auto-immunisation with MUC1 (our group) and a mutual genetic basis (infertility gene is also susceptibility gene for BC).
Pregnancy after BC is not contra-indicated. This is important as age at first pregnancy goes up, while prognosis for women under 40 years with BC improves. BC treatment might induce ovarian failure (chemotherapy) or might impair lactation (radiotherapy). Survival is not negatively influenced, neither are the frequency of local recurrences, nor of distant metastases.

Modern women delay child birth and therefore increase their risk of BC during pregnancy (average frequency 1 in each 5000 pregnancies). On basis of seven prospective and 41 retrospective studies, the following clinical picture emerges. Delay in diagnosis is common, as the mammogram is less sensitive (dense breasts), but safe to the foetus. Abortion is no longer advocated. Histology should be obtained either by fine-needle aspiration or core biopsy. Pregnancy-associated tumours are, on average, larger, more often node-positive and oestrogen receptor (ER)-negative. However, when matched for age and stage, prognosis is not worse. Mastectomy (without postoperative radiotherapy) is preferred by many above lumpectomy (with radiation), both in combination with axillary dissection. Sentinel node procedure with isotopes is considered contraindicated. Chemotherapy (after first semester) and radiotherapy (after delivery) are safe. Tamoxifen during pregnancy is considered a risk. In low-stage patients, subsequent pregnancies are not considered to be contraindicated.

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