Estrogens can enhance the development of breast cancer mainly by stimulating the transcription of genes involved in breast cell proliferation, and by causing DNA damage via their genotoxic metabolites produced during oxidation reactions (1). Moreover, estrogens can: i) induce growth factors and interact with them in a complex manner; ii) activate human telomerase reverse transcriptase [hTERT]; increase the expression of matrix metalloprotease and vascular endothelial growth factor [VEGF] (2-6). The effects of progestins on normal and malignant breast cell growth are contrasting. The mitotic rate of breast cells is higher during the luteal phase of the menstrual cycle than during the follicular phase (7). Progestins have been found to inhibit, stimulate or have no effect on the proliferation of either normal breast epithelium or breast cancer cell lines, depending on type, dose and exposure time (2,8-11). For instance, in vitro studies have shown that progestins derived from 19-Nortestosterone exert an estrogen-like proliferative effect on breast cancer cell lines, and this effect is probably mediated by reduced 5α- metabolites, which interact with α- and β- estrogen receptor [ER]s (8-10). The breast cancer risk associated with hormone replacement therapy [HRT] in postmenopausal women has long been debated (12-16). There is good evidence from observational and randomized trials of an increased risk of breast cancer in women receiving estrogen plus a progestin compared with those receiving estrogen alone. For instance, in the Women’s Health Initiative [WHI] randomized controlled trial (enrolling 16,608 postmenopausal women with intact uterus), women randomly allocated to receive conjugated equine estrogens [CCE] 0.625 mg/day plus medroxyprogesterone acetate [MPA] 2.5 mg/day had an hazard ratio [HR] of breast cancer of 1.26 (95% confidence interval [CI], 1.00-1.59) when compared to those receiving placebo after a mean of 5.2 years of follow-up (12). Conversely in the estrogen-alone component of the WHI study (including 10,739 postmenopausal women with prior hysterectomy), after an average follow-up of 6.8 years women receiving CCE 0.625 mg/day had a HR of breast cancer of 0.77 (95% CI, 0.59-1.01) when compared to those receiving placebo (14). Some studies appear to suggest that progestins with different biological properties could have a different impact on breast carcinogenesis (17-21). In a Swedish population-based case-control study (including 3,345 women aged 50 to 74 years with invasive breast cancer and 3,454 controls of similar age) breast cancer risk was higher among women treated with androgenic progestins, with an increase of 8% for each year of use (17). In a French cohort study 3,175 postmenopausal women, 17,395 of which were HRT users, were followed for a mean of 8.9 years. Eighty-three per cent of HRT received exclusively or mostly a combination of a transdermal estradiol (E₂) gel and a progestin other than MPA (18). One-hundred and five cases of breast cancer were detected during the follow-up period. Multivariate analysis failed to detect an increased risk of this malignancy in HRT users (relative risk [RR], 0.98; 95% CI, 0.65-1.5). In a German case-control study (including 3,593 breast cancer patients and 9,098 controls), current or past use of HRT was associated with a slightly increased adjusted odds ratio [OR] (1.2; 95% CI, 1.1-1.3) of breast cancer, without any significant variation according to HRT formulations (21). As for progestins, only norethindrone acetate showed a slight increase in breast cancer risk estimates. A very interesting investigation on the relevance of the type of progestin used for the HRT is represented by the recent E3N-EPIC cohort study conducted on 54,548 postmenopausal women. (20). During a mean follow-up time of 5.8 years, 948 primary invasive breast cancers were diagnosed. The RR of this malignancy was 0.9 (95% CI, 0.7-1.2) for the women receiving HRT containing micronized progesterone and 1.4 (95% CI, 1.2-1.7) for those using HRT containing synthetic progestins. Recent in vitro and in vivo experimental data appear to confirm that different progestins may exert differential actions on breast cancer cell metabolism and proliferation. By assessing estrogen-metabolizing enzymes in ER-positive human breast cancer cells cultured with E₂ and progestins, Xu et al. (22) found that the MPA +E₂ stimulated the mRNA levels and activities of estrogen-activating enzymes aromatase, 17β hydroxysteroid dehydrogenase type-1, and sulfatase compared to E₂ only, and that progesterone also stimulated enzyme activity, but to a lower magnitude. In a randomized crossover trial performed on 26 ovariectomized adult female monkeys, Wood et al. (23) found that, compared to placebo, the administration of oral E₂ (1 mg/day); + MPA (2.5 mg/day) resulted in a greater proliferation in breast lobular (p <0.01) and ductal (p <0.01) epithelium, whereas E₂ + micronized progesterone (200 mg/day) did not. Moreover,
Ki67 and cyclin B1 expression in breast tissues was higher after treatment with E$_2$ + MPA (p < 0.01) but not after E$_2$ + micronized progesterone, thus suggesting that micronized progesterone has a more favourable effect on risk biomarkers for breast carcinogenesis than MPA. In conclusion, a few data are currently available to determine whether there are clinically relevant differences among different progestins with respect to breast cancer risk. However, recent experimental data as well as early clinical studies appear to suggest that micronized progesterone does not influence breast carcinogenesis. Further basic and clinical investigations on this topic are warranted.

References