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NEWS AND VIEWS

Is breast cancer risk the same for all progestogens?

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Summary

The population-based case–control study CECILE investigated the impact of various menopausal hormone therapy (MHT) products on breast cancer (BC) risk in 1,555 postmenopausal women [1]. The case group ($n = 739$) included incident cases of in situ (!) or invasive BC in postmenopausal women. The control group ($n = 816$) included women from the general population within predefined quotas by age and socio-economic status (SES). While quotas by age were applied to obtain similar distributions by age among controls and among cases, quotas by SES in control women were applied to reflect the distribution by SES of women in the general population in the study area. Data of participants were obtained by a structured questionnaire during in-person interviews, and from pathology reports if applicable, respectively. Women were divided into current and past MHT user. MHTs were classified in estrogen-only therapy (ET), estrogen combined with progestin therapy (EPT) and tibolone. EPT was subdivided in three subtypes according to the progestogen constituent: natural micronized progesterone, progesterone derivatives, and testosterone derivatives. In comparison to never MHT users, any current or past MHT use (ET, EPT, tibolone) was not associated with an increased BC risk. However, in subanalysis BC risk was significantly increased for current use of EPT for 4 or more years ($n = 73$ cases and $n = 56$ controls, adjusted OR 1.55; 95 % CI 1.02–2.36). Within the group of current EPT users for 4 or more years, 14 cases had used estrogens combined with micronized progesterone ($n = 17$ controls), and 55 a combination with a synthetic progestogen ($n = 34$ controls), respectively. Compared to never MHT use, current use of EPT containing a synthetic progestogen for 4 or more years was associated with a significantly increased BC risk (adjusted OR 2.07; 95 % CI 1.26–3.39), but EPT containing micronized progesterone was not (adjusted OR 0.79; 95 % CI 0.37–1.71). 73 % of current MHT users started treatment within the first year of onset of menopause. Early EPT ($n = 52$ cases and $n = 38$ controls, adjusted OR 1.65; 95 % CI 1.02–2.69), but not early ET, starters had a significantly higher BC risk compared to never MHT users. In contrast, MHT initiation beyond 1 year after menopause was not associated with an increased BC risk. The authors concluded that: (1) ET and EPT containing natural progesterone did not increase BC risk whereas, (2) BC risk was increased in users of tibolone or EPT containing a synthetic progestogen, respectively, and that (3) MHT use early after onset of menopause was associated with an increased BC risk as compared to women who delay MHT beyond 1 or more years.

Background

The primary indication for MHT is vasomotor symptom control [2]. In women with an intact uterus systemic estrogens should be combined with a progestogen (natural progesterone or synthetic progestin) for endometrial protection. Since the initial report of the Women's Health Initiative in 2002 indicating an increased BC risk associated with the use of conjugated equine estrogens combined with medroxyprogesterone acetate (MPA) [3], there is a tremendous debate about whether all progestogens have the same negative impact on the postmenopausal mammary gland when combined with estrogens. Basically progestogens

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only have one effect in common, i.e., the progestogenic effect on the estrogen-primed endometrium [4]. Apart from that, there are large differences between progestogens with respect to other normal or malignant cells and tissues such as the mammary gland, respectively [5, 6]. So far there are four observational studies suggesting that the use of MHT containing progesterone or dydrogesterone, a stereoisomer of progesterone, is "safer" for the breast than using MHT containing synthetic progestins [7–10]. Of those, the prospective French E3N cohort study has been the largest trial to address BC risk with respect to progestogen type in combined MHT. Compared with MHT never use, BC risk was increased with MHT containing "other" progestogens (adjusted RR 1.69; 95 % CI 1.50–1.91) but not with those containing progesterone (adjusted RR 1.00; 95 % CI 0.83–1.22) or dydrogesterone (adjusted RR 1.16; 95 % CI 0.94–1.43), respectively [9]. Similarly, a German case–control study only found an increased BC risk for use of norethindrone acetate containing MHT, for more than 5 years but not for other progestogens [11]. Long-term randomized placebo-controlled trials in humans investigating the impact of various combined MHT on the breast are lacking. However, in non-human primates a randomized crossover trial in ovariectomized cynomolgus macaques was performed comparing the impact of estradiol (E2), E2 combined with progesterone, E2 combined with MPA to placebo on breast epithelial proliferation [12] and mammary gene expression profiles [13]. Compared to placebo, E2 combined with MPA resulted in significantly greater breast proliferation in lobular and ductal epithelium, while E2 combined with progesterone did not [12]. Gene microarray analysis resulted in a greater number of significantly regulated genes for E2 combined with MPA when compared to E2 combined with progesterone and E2 alone with progesterone revealing greater antagonistic effects on E2-induced genes than MPA [13], which was supported by a small study in humans [14]. All these findings taken together suggest a more favorable effect for micronized progesterone and dydrogesterone on postmenopausal mammary gland.

Comment

The retrospective case–control study CECILE (LoE II-2) picks up the current exciting subject on the impact of progestogen type on the mammary gland. At first sight, it supports previous findings from the prospective E3N study indicating that estrogens combined with micronized progesterone are "safer" for the postmenopausal mammary gland. However, a closer look reveals some limitations. First, the statistical analysis was based on small sample sizes. Indeed, the primary endpoint important for power calculation was not given and the authors themselves argued that the statistical power might have been limited for stratified analyses. Second, dosage and route of administration of progesterone were not assessed which might have an impact of BC incidence [6]. Next, cases included in situ and invasive BC, and the authors did not present the respective absolute numbers. However, ductal carcinoma in situ (DCIS) is a non-obligate precursor of invasive BC with "only" 40 % of these lesions progressing to invasive disease if untreated [15]. Therefore, the analysis should have been stratified with respect to in situ and invasive BC, respectively. Finally, there is a potential confounding by SES since control selection was based on SES within the population of the study area and not on BC cases.

Taken together the CECILE study serves as another hint indicating a favorable mammary profile for MHT containing progesterone. However, more evidence is needed. In respect to tibolone, the authors surprisingly commented on their results that "tibolone was also associated with an increased risk of BC" contradicting the Endocrine Society's statement that "tibolone reduces the risk of developing BC (LoEB)" [16]. In fact, absolute numbers for any duration of current ($n = 17$ cases, $n = 8$ controls) and past tibolone users ($n = 10$ cases, $n = 15$ controls) were very small. Statistical analysis did not reach significance at any time. Thus, interpretation should be more softened. Interestingly, the time gap between menopause and MHT initiation mattered which supports previous observations that delaying MHT onset for a certain, but yet undefined interval seems to be beneficial for the postmenopausal breast [17–19] which needs further investigation.

Conflict of interest None.

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