We declare that we have no conflicts of interest.

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Untangling *BRCA* mutations, sex hormones, and cancer risk

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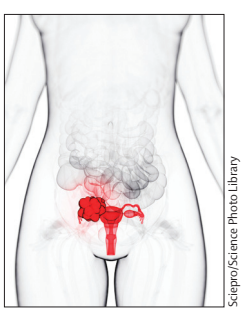
Understanding basic disease mechanisms might allow development of novel strategies for the primary prevention of breast and ovarian cancer. For carriers of *BRCA1/2* mutations, options for primary prevention are limited to bilateral salpingo-oophorectomy and prophylactic mastectomy. In *The Lancet Oncology*, Martin Widschwendter and colleagues[1] compare ovarian and endometrial function in carriers of the *BRCA1/2* mutation with high-risk, mutation negative women in the UK Familial Ovarian Cancer Screening Study. *BRCA1/2* mutations are thought to cause cancer via a defect in DNA damage response or in the DNA repair pathway, but this does not explain organ-specific cancer penetrance. These novel data suggest that end-organ response might have a role.

Using endometrial thickness measurements collected during transvaginal ultrasound to detect ovarian cancer, cross-sectional data showed that premenopausal women carrying the mutation (n=203 scans in 116 *BRCA1*-positive women and 190 in 112 *BRCA2*-positive women) had a thicker endometrium in the follicular phase and a thinner endometrium in the luteal phase than did controls (n=1573 scans in 754 women). Using existing blood samples from a small number of women carrying the *BRCA1* (n=38) and *BRCA2* (n=32) mutations, the investigators did not identify any differences in circulating concentrations of oestradiol and progesterone in the follicular phase, but concentrations of both hormones were higher in the late luteal phase (days 21–26) compared with 339 controls. The investigators propose that this relates to a defect in steroid-hormone regulation, which potentiates the mutagenic effect of the *BRCA1/2* mutation and explains the organ specific penetrance of malignancies.

An important limitation of this approach is using endometrial thickness as a marker of hormone regulation. How endometrial thickness was measured is not defined. Endometrial ultrasound is highly user-dependent. Scans were done at 44 different sites but no data on reproducibility were reported. Normal premenopausal endometrial thickness varies substantially. It is increased during the follicular phase, plateaus around ovulation, and remains stable throughout the luteal phase.[2] This variation does not support the assertion that in women carrying the *BRCA1/2* mutation a thinner endometrium and higher luteal concentrations of oestradiol and progesterone are in complete concordance. Unlike exogenous progestogens, luteal progesterone does not typically induce a thin endometrium.[3]

It is also unclear how menopausal status was defined. Participants were younger than 50 years, but menstrual irregularity starts at a median age of 47 years, and participants with anovulatory cycles would have notably different endometrial thickness and circulating sex steroids.[4] Exogenous sex steroids would also affect all measures but present use was not recorded.

Higher circulating oestradiol in carriers of the gene mutation is consistent with general population data associating higher oestradiol with premenopausal breast cancer risk.[5] The proposed relation with higher



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See **Articles** page 1226

progesterone concentrations is less convincing. Unlike testosterone levels, progesterone concentrations are not associated with breast cancer risk in premenopausal women.[5] Recent pilot data suggest that *BRCA2* carriers with breast cancer have marginally higher oestradiol concentrations in the early follicular phase than do *BRCA1* or mutation negative women.[6] Preclinical data in *Brca1* mice suggest increased circulating and endometrial proliferation in proestrus.[7] Recent data[8] do not support the speculation that women carrying the *BRCA1/2* mutation have an earlier age at menopause.

Combining data from carriers of the *BRCA1* and *BRCA2* mutations in the present study was justified as a measure to increase statistical power, but might have obscured key endocrine differences pertinent to variations in cancer risks. It is unclear why a gene mutation affecting DNA repair should affect ovarian sex steroid production in the late luteal phase and this needs further investigation. Both endometrial and sex steroid measurements were cross-sectional, making it impossible to infer within-cycle sex steroid or endometrial differences in *BRCA* carriers.

These data are novel in combining ovarian and endometrial functional data in women with the *BRCA1/2* mutation. The clinical importance is the potential for modulating ovarian sex steroid production to reduce cancer risk. Ovarian suppression with the oral contraceptive pill reduces ovarian but not breast cancer risk in *BRCA1/2* mutation carriers.[9] It is unclear why exogenous sex steroids in the contraceptive pill should be protective, if endogenous sex steroids increase risk. Targeted therapies inhibiting oestrogen and HER2 are established in breast cancer treatment. Clarifying the role of progesterone might suggest a role for selective progesterone receptor modulators such as ulipristal.[10] It is certainly premature to suggest that sex steroids are one of the major drivers for development of breast cancer in this population. Although of interest, cross-sectional studies can only provide limited information on relations in inherently dynamic pathways. The complex relation between gene mutations, ovarian cancer risk, endocrine function, endocrine production, and receptivity in *BRCA1/2* mutation carriers still need to be established. These provocative findings might open a new direction in mechanistic studies that increase understanding of cancer mechanisms in high-risk women.

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Axitinib dose titration: what's the limiting factor?

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See **Articles** page 1233

Pharmacokinetic data suggest that for patients with metastatic renal-cell carcinoma an increased exposure to tyrosine kinase inhibitors could be associated with improved clinical outcome.[1,2] To date, four approaches to increase drug exposure have been proposed. First, simple dose escalation until unacceptable toxic effects is reached (a strategy which has ultimately failed);[3-5] second, changing the schedule from the beginning of treatment, or according to toxicity;[6-8] third, adapting the dose according to evidence of specific polymorphisms in genes involved in drug pharmacokinetics;[1] or, fourth, dose titration in