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Disruption of androgen receptor signaling by synthetic progestins may increase risk of developing breast cancer

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There is now considerable evidence that using a combination of synthetic progestins and estrogens in hormone replacement therapy (HRT) increases the risk of breast cancer compared with estrogen alone. Furthermore, the World Health Organization has recently cited combination contraceptives, which contain synthetic progestins, as potentially carcinogenic to humans, particularly for increased breast cancer risk. Given the above observations and the current trend toward progestin-only contraception, it is important that we have a comprehensive understanding of how progestins act in the millions of women worldwide who regularly take these medications. While synthetic progestins, such as medroxyprogesterone acetate (MPA), which are currently used in both HRT and oral contraceptives were designed to act exclusively through the progesterone receptor, it is clear from both clinical and experimental settings that their effects may be mediated, in part, by binding to the androgen receptor (AR). Disruption of androgen action by synthetic progestins may have serious deleterious side effects in the breast, where the balance between estrogen signaling and androgen signaling plays a critical role in breast homeostasis. Here, we review the role of androgen signaling in the normal breast and in breast cancer and present new data demonstrating that androgen receptor function can be perturbed by low doses of MPA, similar to doses achieved in serum of women taking HRT. We propose that the observed excess of breast malignancies associated with combined HRT may be explained, in part, by synthetic progestins such as MPA acting as endocrine disruptors to negate the protective effects of androgen signaling in the breast. Understanding the role of androgen signaling in

the breast and how this is modulated by synthetic progestins is necessary to determine how combined HRT alters breast cancer risk, and to inform the development of optimal preventive and treatment strategies for this disease.