The Female Prostate

Contrary to the statement by Borchert et al. *(1)* that ''Women have no prostate . . . ,'' women do have a prostate, the presence of which has clinical significance for the female and for our understanding of the expression of prostate-specific antigen (PSA) in women and its possible implications.

In 1672 the anatomist Regnier de Graaf described and illustrated a set of glands and ducts surrounding the female urethra that he called the female prostate. Subsequently, in 1880, Alexander Skene redirected attention to this structure, particularly to two paraurethral ducts (Skene's ducts) therein, and emphasized their importance in infection of the female genitalia.

Skene's paraurethral glands and ducts are homologous to the male prostate *(2)*. Recent studies supporting this homology, as reviewed by Zaviačič et al. *(3,4)*, are postmortem and detailed histological examinations of the urethras of 130 women, followed by biochemical and immunohistochemical studies that demonstrated expression of PSA and prostate-specific acid phosphatase (PSAP) in Skene's paraurethral glands and ducts. These studies unequivocally substantiate the existence of the female prostate.

The female homologue of the male prostate is of clinical significance not only as a focus for acute and chronic infection, but also as the origin of other pathologic entities, including adenocarcinoma *(3,4)*, a cancer which shows, as does its male counterpart, localized expression of PSA and PSAP *(3,4)*.

Thus, there is convincing evidence that prostatic tissue exists in the female, and that the term ''female prostate'' is both fully justified and preferable to the terminology Skene's glands and ducts. The latter incorrectly implies that some other structure of an extraprostatic nature, rather than the prostate itself, is involved. If the female prostate exhibits the immunopermissiveness observed in the male prostate *(5)*, it may also serve as a site for viral latency and origin of infection in women with human immunodeficiency virus.

Of perhaps equal importance is the expression of PSA *(6)*. The existence in women of the counterpart of the male prostate, shown to express PSA, may provide a note of caution in considering the molecular basis of the apparent anomalous expression of PSA in male and female nonprostatic tissues, e.g., in female breast *(1)*. Given observations on the association of PSA detection in breast cancer with steroid hormone-receptor positive tumors, one may envision *(6)* the existence of a complex regulatory gene network controlling the expression of PSA in several organs. Therefore, a given tissue (depending on the state of cellular differentiation) may express previously repressed genes after neoplastic transformation. Also, and not mutually exclusive, somatic mutations may lead to specific changes in PSA genes in cancer cell clones *(6)*.

Consider also, as initially pointed out by Longo *(7)*, the forensic implications for alleged cases of rape. In the absence of knowledge of the female prostate and of the possible presence of PSA and PSAP in the normal female ejaculatory fluid, the identification of these supposedly male-specific markers in vaginal secretions may have been ''. . . a *fait accompli*'' *(7)* to the accused, but possibly innocent, perpetrator. Indeed, judicial miscarriage may have easily occurred when, for example, PSAP has been considered adequate for the identification of sperm spots and its potential origin from the prostate of the female victim was not taken into account. Therefore, the presence of PSA and/or PSAP for the confirmation of spermatic secretion in the absence of spermatozoa has no forensic value. This knowledge of PSAP originating from the female ejaculate was instrumental in the recent acquittal of an alleged rapist in Europe. In this regard, forensic DNA analysis can be expected to play a significant role in the near future.

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Response

Zaviačič and Ablin want to use the term ''female prostate'' to describe what is widely known as the Skene's glands and ducts, a terminology that I do not oppose. In addition to the literature provided, others have also made such suggestions in the past *(1)*. One of the biochemical similarities between male prostate tissue and Skene's gland tissue is the expression of prostate-specific antigen (PSA). Indeed, PSA has been immunohistochemically localized in Skene's gland tissue by a number of investigators. However, it should be pointed out that female tissue other than the Skene's gland can produce PSA. Normal female breast epithelial cells produce relatively large amounts of PSA and secrete it into the lumen of the mammary ducts. A small portion of this PSA escapes into the general circulation and can be measured with highly sensitive techniques.

A misconception in the letter by Zaviačič and Ablin is the notion that PSA is expressed by breast tumors as part of the neoplastic transformation process. Originally, our group had discovered PSA expression in a subset of breast tumors that were more frequently steroid hormone receptor-positive *(2)*. Subsequent studies have indicated that PSA

is expressed not only by breast tumors but by normal and hyperplastic breast tissue as well *(3)*. In fact, hyperplastic breast tissue contains more PSA than either normal or cancerous breast tissue, and the same applies to the serum PSA in women with these conditions *(4)*. Importantly, PSA has been found in all breast secretions, including breast cyst fluid, the milk of lactating women, and nipple aspirate fluid. The concentration of PSA in nipple aspirate fluid can reach levels up to 3000 μg/L, about 1000 times higher than in male serum *(5)*. PSA concentration is higher in the nipple aspirate fluid of women with no risk for breast cancer and significantly reduced in breasts with cancer *(5)*. We thus conclude that PSA is a normal secretory product of the breast epithelial cells. Some well-differentiated and receptor-positive breast tumors retain the ability to produce PSA.

PSA regulation in the breast is mediated through the steroid hormone receptor system *(6)*. Androgens and progestins—and, to a lesser extent, glucocorticoids and mineralocorticoids—upregulate this gene. These findings were confirmed both in tissue culture systems and in humans who received exogenous steroid hormones, including oral contraceptives.

The expression of PSA in the female breast is quite significant and should not be considered a minor event without physiological importance *(7)*. Since PSA is a proteolytic enzyme, it may be fruitful to examine if there is a substrate for it in breast tissue. Other investigators point out the possibility that PSA may be a growth factor or a cytokine regulator *(7)*. Furthermore, PSA is not even a specific marker for male/female prostate and breast tissue. We have demonstrated PSA expression in lung, ovarian, and other tumors. At this point, it is fair to suggest that PSA is expressed by many tissues that are responsive to steroid hormones, but that the predominant sources are the prostate in males and the breast in females. The biochemical connection, if any, between PSA expression in the female breast and breast cancer remains to be elucidated.

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