Model Systems for Cervical Cancer

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Summary

The evidence suggesting that a venereally transmitted virus and/or hormonal factors are involved in the etiology of cervical cancer is reviewed. The animal models used to test the oncogenic potential of these two types of agents are also discussed.

In the search for animal model systems for cervical cancer we should keep in mind that we are dealing with a multifactorial event, as is probably the case with all human tumors. It is therefore most unlikely that we will be able to identify a single causative factor that is uninfluenced by other factors. After reviewing some basic epidemiological facts of cervical cancer, the following conclusions could be drawn (7, 16).

1. Sexual intercourse is a necessary but not sufficient event in the genesis of squamous cell carcinoma of the cervix. Sexual intercourse could eventually lead to cervical cancer by making possible the transmission of a carcinogen by the penis to the susceptible cervix and/or by introducing changes in female organisms (such as hormonal changes), which would make the uterine cervix susceptible to a given carcinogen.

2. The venereally transmitted carcinogen could be a chemical or an infectious agent. No chemical carcinogen has been identified so far in the smegma or semen. Although there is some experimental evidence suggesting a weak carcinogenic effect of smegma on the cervix of the mouse (15), there is little epidemiological support for a carcinogenic effect of smegma on the human cervix (10). Among infectious agents, trichomonas, syphilis, and HSV-2 have been associated with cervical cancer, but the nature of this association remains unknown (2). Besides HSV-2, other viruses are known to cause infections of the uterine cervix: CMV and the papilloma virus of condyloma acuminate. The evidence linking HSV-2 to cervical cancer is reviewed later in this symposium.

Although CMV is a common cause of chronic cervicitis (2), it is isolated more frequently than HSV-2 in venereal disease clinics (6), and has been recovered in high titers from semen (8), few studies have investigated the possible association between this virus and cervical cancer. The few seroepidemiological studies that have been done yielded controversial results. Moreover, an association between cervical cancer and CMV should be even more difficult to establish by seroepidemiological analysis than it is with HSV-2 because the venereal route is probably not as common a route of transmission as the p.o., parenteral, and transplacental routes, and because no genital strain of CMV has been characterized so far. Experimentally, a transforming potential has been demonstrated in hamster embryo fibroblasts (1).

Only recently, a papilloma virus was satisfactorily demonstrated in genital warts or condyloma acuminate. This lesion is interesting because transformation into squamous cell carcinoma has been reported (17), but no studies relating this virus to cervical cancer have been reported to date.

3. If a carcinogen is venereally transmitted, a set of predisposing conditions should be necessary for the eventual development of cervical cancer. Among the predisposing conditions or cofactors that we might consider are hormonal factors, alterations in the immune response, and genetic susceptibility.

Viruses and Hormones Tested for Carcinogenicity in Animal Models

Viruses. Among the venereally transmitted viruses, only HSV-2 has been tested in different models. Nahmias et al. (12) and Muñoz (11) reported that infection of the human cervix with HSV-2 occasionally induced cervical atypia or carcinoma. Nahmias et al. (13) reported that inoculation of hamsters with 16 strains of HSV-2 by different routes resulted in the induction of few sarcomas at the site of inoculation. Larson et al. (9) showed that rabbits are susceptible to intravaginal inoculation with HSV-2, but no cancers were observed because all animals died shortly after inoculation. In this symposium, Dr. Palmer (15) describes experiments with monkeys.

Hormonal Factors. Natural and synthetic estrogens have been tested in several animal species (5). In mice, administration of estrogens by different routes resulted in an increased incidence of endometrial adenocarcinoma, mammary, pituitary, lymphoid, and interstitial cell tumors. Estrogen administration in rats was associated with an increased incidence of pituitary, mammary, bladder, and liver cell tumors. In hamsters, estrogens produced an increased incidence of renal tumors. Diffuse abdominal fibromatosis was induced in guinea pigs by these hormones. Malignant mesothelioma of the uterine serosa and adenocarcinoma of the breast have been reported in monkeys.

Progesterone, when given alone, increased the incidence of ovarian, uterine, and mammary tumors in mice. When given in combination with known carcinogens, it increased...
the incidence of tumors produced by these carcinogens. Synthetic progestins have some carcinogenic potential in animal systems even when administered alone.

In general, it appears that steroids increase the probability of tumor development in those tissues normally responsive to stimulation by such steroids.

**Comparative Aspects of Humans**

Experimental cervical carcinoma has been reported only in mice. Although cervical cancer is extremely rare in untreated mice but relatively frequent in women, the morphology of the neoplasm in the 2 species is remarkably similar. However, there are differences in the process of carcinogenesis. Whereas the transition from dysplasia to carcinoma in situ to invasive carcinoma seems to be frequent in women, it appears to be extremely rare in mice. The most frequent change observed during the process of carcinogenesis in mice is the formation of epithelial processes that progressively infiltrate the connective tissue. The cancers in both species are squamous cell carcinomas, but cancers in mice, unless the cervix is directly exposed to chemical carcinogen, are well differentiated with limited infiltration and no or few metastases. This is in contrast to the undifferentiated, highly malignant, and metastasizing tumors that are often observed in women.

From the etiological point of view, the role of viruses in the development of cervical cancer in mice and women remains unclear. The role of steroid hormones, on the other hand, appears to be more important in the genesis of cervical cancer in mice than in women. However, we should keep in mind that epidemiological studies to determine the role of steroid hormones in human cancer are difficult to conduct, because the latent period in cancer is long and because observations in a very large number of individuals are required to detect small or moderate changes in the cancer risk. Despite these limitations, it has been shown that administration of diethylstilbestrol to women during pregnancy is associated with an increased risk of vaginal or cervical adenocarcinoma in their exposed female offspring (4). There is also evidence that suggests that women with gonadal dysgenesis treated with diethylstilbestrol have an increased risk for endometrial adenocarcinoma (3) and that men treated with the same drug for carcinoma of the prostate have an increased risk of breast cancer (14). On the other hand, oral contraceptives have not as yet been shown to alter the risk for cancer of the breast, and the evidence with respect to cervical cancer is less consistent (5).

Studies on genetic susceptibility to infectious agents, which have been proposed as etiological candidates, could further our understanding of the nature of the association between these infectious agents and cervical cancer.

**References**

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