A Selective Review of Experimental Studies in Cervical Carcinoma

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Summary

With various human clinical, epidemiological, and experimental data together with basic carcinogenesis experimentation, a working hypothesis of the development of cervical cancer is presented. Initiation may involve a carcinogen (perhaps herpesvirus type 2) altering the susceptible metaplastic cervical cell that is active in adolescence and during pregnancy. Promotion by factors perhaps related to coitus or to the continued metaplastic process in a field of abnormally mitosing cells allows for selection of a clone of cells with the characteristics of unlimited growth and invasion.

Human cervical cancer and its antecedent lesions (dysplasia and CIS\(^1\)) offer a unique opportunity to study the pathogenesis of a human neoplasm. The cervix is a common site of neoplastic change, it is readily accessible so that preinvasive lesions may be accurately diagnosed, and there is a wealth of epidemiological and experimental data relating to the spectrum of this disease. The recent experiments exploring the possible association of herpes simplex virus type 2 and cervical cancer must be applied to the wealth of clinical and experimental data on cervical cancer, CIS, and dysplasia. The opening session of the Symposium on Herpesvirus and Cervical Cancer was designed to acquaint the participants with some of the experimental studies and theories related to the development and progress of cervical cancer. This paper is an attempt to utilize some of these experimental data to develop a working hypothesis that may be useful in explaining the relationship between dysplasia, CIS, and invasive cervical carcinoma. This relationship between the various phases in the spectrum of cervical neoplasia may allow a more intelligent speculation and hopefully may be followed by the investigation of the mechanism that the herpesvirus might have in relation to the disease.

Clinical Studies

The key question in the study of early cervical neoplasia is the relation of dysplasia, particularly the early forms, to the remainder of the spectrum of the disease, i.e., CIS and invasive carcinoma. The fact that CIS will progress to invasive cancer if left undisturbed is generally accepted. One may review the findings that led to this conclusion in the Conference on Early Cervical Neoplasia (7) also sponsored by the American Cancer Society.

Dysplasia appears to be the early part of the continuum leading to invasive cervical cancer. The patients with dysplasia have most of the same epidemiological characteristics of the patients who have CIS and invasive cancer, as has been mentioned earlier in this Conference. Serological data of antibodies to herpesvirus type 2 in patients with dysplasia, CIS, and invasive cancer are also similar (24) and are discussed in more detail later in the Conference. Anatomically, the lesions of dysplasia and CIS occur at the same location on the cervix and indeed, at times, are difficult to differentiate (8, 20, 31). Almost always areas of dysplasia occur adjacent to areas of CIS.

The most definitive human "experiment" would be that in which one follows patients with dysplasia and observes the outcome over a period of time. The problems of such a study mainly revolve around being able to follow these lesions without either removing them completely or disturbing them (20, 21). The lesions of dysplasia may be very small (sometimes only 30 cells in diameter) and easily removed by a single punch biopsy (20, 31). The biology may be significantly altered by a biopsy, even if the lesion is not completely removed. The study by Richart and Barron (21) is the largest and most definitive study using the strict criteria of 3 positive Papanicolaou smears of dysplasia for entrance into the study. Only 6 of 577 patients regressed spontaneously and all of these were from the minimal dysplasia category. Most progressed to more advanced degrees of dysplasia or CIS, with 3 patients progressing to early invasion. The authors (6) presented convincing statistical analysis and an interesting theoretical model to substantiate these observations. Fox (10) had no regressions in a similar group of patients with severe dysplasia or CIS, but he did note regression in some patients with mild dysplasia, although the admission requirements were not as rigid and the follow-up was not as consistent as Richart's. Preliminary data from a study at Duke University School of Medicine designed to follow patients with dysplasia without biopsy indicate that early dysplasia may be intermittent but once it becomes established most mild lesions tend to progress to severe dysplasia or CIS if left undisturbed (G. D. Wilbanks, unpublished data). The excellent epidemiological data of Stern and Neeley (30) corroborate these theories in that virtually all patients who developed CIS in a previously screened population came from those patients with dysplasia.

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\(^1\) Presented at The American Cancer Society Conference on Herpesvirus and Cervical Cancer, December 8 to 10, 1972, Key Biscayne, Fl.

\(^2\) The abbreviation used is: CIS, carcinoma in situ.
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Careful anatomical observations by many investigators add plausibility to some of the epidemiological and other general data. The lesions of early cervical neoplasia occur in the transformed squamous epithelium (transformation zone of the colposcopist). Copplonsen and Reid (8) equate the activity of this area at adolescence and during pregnancy (especially when the 1st pregnancy occurs at a young age) with the apparent epidemiological importance of these events (29). Others (7, 20) have likened this new epithelium to the promotion-like effect of wound healing in the classic initiation-promotion animal chemical carcinogenesis experiments. It has also been suggested that this regenerating epithelium is more sensitive to an initiating event (8, 20). The disappearance of lesions after incomplete excision or other incomplete treatment, the peculiar anatomical configuration of the lesions, and some observations after experimental biopsies suggest the reason for “regression” of some of these lesions in reported series (20, 21) and caused speculation regarding an epithelial chalone that was operative at the cervical squamocolumnar junction (7).

Animal models of chemical carcinogenesis of the cervix lend credence to the observed progression of these lesions in humans, as these animal cancers go through progressive stages of dysplasia and CIS, to invasive tumors (11, 12, 26). Currently, animal studies of herpesvirus type 2 cervical carcinogenesis are in progress, but no significant data are available yet (14, 17).

Laboratory Studies

Studies utilizing incubation of tissue slices of dysplasia and CIS (9, 19) showed a progression of uptake of tritiated thymidine by increasing grades of severity of dysplasia and CIS. Averette et al. (4) have also noted altered tritiated thymidine uptake by human in vivo studies of CIS and invasive cervical cancers. There is an abnormal DNA amount and chromosome number and karyotype in even the mild dysplasias (1, 2, 13, 20, 32). Some (2, 32) have advocated the use of chromosome studies to differentiate between dysplasia (with neoplastic potential) and nonneoplastic metaplasia or hyperplasia. Dysplasia and CIS display a wide range of DNA amount and chromosome number, while with invasion these ranges tend to narrow to certain “stem cell” lines (1, 5, 15).

In tissue culture, the cells from dysplasia and CIS seem to behave in a manner intermediate between normal cells and invasive cancer (33). Consistent abnormalities in mitotic behavior of cells from dysplasia and CIS have been observed (22). Prophase and telophase were significantly prolonged, perhaps explaining the wide spread of DNA and chromosomes observed in these lesions by the irregular arrangements of the chromosomes during this prolonged prophase period. Transformation in vitro of animal cells by chemical carcinogens and viruses has been described by many researchers. Munk and Darai (16) present a report regarding transformation of fibroblasts with herpesvirus type 2, in vitro, at this Conference. Preliminary studies (33) of transformation of human cervical epithelial cells by chemical carcinogens in vitro have not been confirmed, and thus far transformation in vitro of human cervical cells with herpesvirus type 2 has been unsuccessful (G. D. Wilbanks, unpublished data).

The report (3) of isolation of a herpesvirus type 2 from a culture of cells from CIS is interesting, as are the findings of antibodies on the surface of exfoliated cells (25). Roizman and Frenkel’s preliminary report (23) at this Conference of the identification of a portion of herpesvirus type 2 DNA in a cervical carcinoma stimulates further research in these directions.

At the ultrastructure level, no viral particles have been identified in cells from dysplasia, CIS, or invasive cervical cancer. However, Nordquist et al. (18) found DNA virus-like particles in Bowen’s disease of the skin and even isolated a virus from these lesions. The cells from dysplasia and CIS have similar changes in the nucleus, cytoplasm, and surface, but they differ from normal cervical cells in biopsy and in vitro specimens (27, 28). The increase in number and length of microvilli seen in dysplasia and CIS is also seen in vitro in cells infected with herpesvirus type 2 (34).

Speculation

To develop a theory (hypothesis) regarding the occurrence of invasive cervical carcinoma through varying stages of development, it is necessary to organize these varied observations into a logical scheme. The initiating factor might be the herpesvirus type 2, or other carcinogens, that gain access to cervical cells that are especially susceptible during the active squamous metaplasia occurring during adolescence or with pregnancy at a young age. Promotion could occur by repeated exposure to the original initiating agent, other promoting agents associated with coitus, or simply the repeated healing processes involved with the formation of the transformed epithelium. During “promotion” there is the increase in mitotic activity and an increase in abnormal mitoses. In spite of action of an epithelial chalone and other body regulatory mechanisms (immunological, etc.), eventually a stem cell occurs that has the ability to continue to reproduce and invade and that is tolerated by or overcomes the immunological mechanisms of the bodies, and frank cervical carcinoma occurs.

Although there are deficiencies and alternatives to this hypothesis, it does fit many of the current clinical, epidemiological, and experimental observations. As additional data are accumulated, the hypothesis can be modified, but it may serve as a working base.

References

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