"Screening is only the first half of the equation. Knowledge of and access to effective treatment options are required to complete the equation."

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CHAPTER

4

Diagnosis, Treatment and Prevention

Improvements in Care

With the widespread use of colposcopy, improved techniques for excisional therapy and aggressive treatment of preinvasive lesions, invasive cervical cancer has decreased over the past twenty years. Future research should enable us to prevent this disease through vaccination and a greater understanding of nutrition's role and of the benefits of tobacco control for women.

Diagnostic Procedures and Treatment Modalities

Colposcopy

Colposcopy is the procedure of viewing the cervix, vagina, and vulva with a magnifying lens (colposcope) to identify abnormal epithelial patterns. The colposcopy procedure begins by wiping away cervical mucus with normal saline. Inspection of the cervix is done with a colposcope that magnifies the tissue with filtered and unfiltered light. A 3% - 5% acetic acid solution is then applied to the cervix and upper vagina. The solutions may cause burning or irritation. These areas are then reinspected. If an epithelial abnormality is identified, a biopsy is done. If the entire lesion is not visualized, an endocervical curettage is indicated. Following a cervical biopsy, either Monsel's solution or silver nitrate may be applied to the cervix with pressure to control bleeding. If done, this can result in a muddy or brownish discharge.

If a biopsy shows either persistent LGSIL or HGSIL, or if there is a question of invasive cancer, further evaluation and/or treatment is indicated. Therapeutic modalities are both ablative and excisional. The ablative techniques include laser and cryosurgery. The excisional modalities include cold knife conization, laser conization, loop electrocautery excision, and hysterectomy.

Ablative Techniques

- **Laser Ablation** Laser ablation is a procedure in which a carbon dioxide laser directed through a microscope is used to vaporize the cervical transformation zone. The procedure is done under local anesthetic and takes 15 to 20 minutes to perform. Post-therapy, the patient may experience some uterine cramping and bloody discharge/vaginal spotting.

- **Cryotherapy** Among ablative techniques, cryotherapy is a procedure performed under direct visualization in which a probe is placed against the cervix. The probe freezes the affected tissue, which in turn results in the destruction and sloughing of cervical cells. The entire procedure takes about 15 minutes. During the procedure, the patient may experience uterine cramping. Subsequently, the patient may expect to have a profuse watery discharge for 7 to 10 days.

Excisional Techniques

- **Electrosurgical Excision (LEEP)** Electrosurgical excision of the transformation zone is a procedure in which an electrical current generating a radio frequency is passed through a wire loop which excises the tissue and cauterizes the base. The procedure usually can be performed in an outpatient setting with the use of local anesthetic.

  Depending upon the size of the loop and the lesion, either the transformation zone or a "cone-like" specimen can be obtained. The patient must be grounded for safety purposes, because an electrical current is used. The electrical current also generates heat, which can cause distortion of the surgical margins, thus making accurate interpretation of the regions difficult, if not impossible. Risks of all excisional procedures include bleeding, cervical stenosis, cervical incompetence, decrease in cervical mucus, and possible infertility.

- **Laser Conization** Laser conization is an operative procedure requiring an anesthetic in which the carbon dioxide laser is used as a knife to generate the same type of specimen obtained with cold knife conization. Postoperatively, the patient will experience cramping and some bleeding.

- **Cold Knife Conization** A cold knife conization (CKC) is an operative procedure requiring either a regional or general anesthetic. During the procedure, the involved ectocervix and endocervix are excised using a circumferential excision. Postoperatively, the patient may have cramping and bleeding. Post-operative infection requiring antibiotic therapy also may occur.

Follow-Up for Excisional /Ablative Treatment

Following excisional/ablative treatment, a woman will need a follow-up Pap smear in three to four months. If the cytology report is normal at subsequent visits, the Pap smear should be repeated every six months for the first two years and then annually thereafter as long as the cervical smear is normal. If, however, a cervical smear is reported abnormal (based upon the Bethesda Classification), the patient should be reintroduced into the observation/treatment protocol.

Hysterectomy

Historically, hysterectomy was performed either vaginally or abdominally for CIN III of the cervix. Currently, with the advent of colposcopy and good excisional therapy, hysterectomy is indicated in only 5-10% of patients.

There are still situations where hysterectomy is acceptable management of the patient. In the presence of the more aggressive recurrent high-grade squamous intraepithelial lesions (HGSIL) in women who have coexisting gynecologic disease and have completed childbearing, hysterectomy may be an option.

If hysterectomy is performed for cancerous lesions, the patient's postoperative follow-up care should include a vaginal smear of the upper 1/3 of the vagina every six months for two years and then annually. Once the patient has had her first postoperative return visit (which should occur within six weeks of treatment), she should follow an observation or follow-up protocol.

Tracking Systems

Impacts on Appropriate Follow-up Care

Tracking is the act of effectively following a patient to assure that appropriate care is provided. Tracking is appropriate for individuals with identified disease and precursors to disease and for other individuals for whom rescreening is recommended. The mechanism for following many individuals in an organized manner is a tracking system.

An ideal tracking system takes into account the interdependence of the health care provider, clinic, laboratory, and patient. In addition to organizing information, the system must also ensure processes for communication among these entities. Communication includes sending, receiving, and understanding relevant information and is, therefore, critical to the success of screening efforts.

Paper Versus Computerized Electronic Data Base

For many years, handwritten tickler files and logs were used for tracking. More recently, these paper systems have been replaced or supplemented by electronic systems. The information in these electronic systems ranges from a very small amount (e.g. a tickler card system) to extensive data (e.g. lifetime medical records). With telecommunications technology, timely communication among appropriate parties is possible, and communication with patients is prepared and documented more readily.

Electronic systems surpass paper systems in their potential usefulness, timeliness, flexibility, and in most cases, acceptability. However, for many users, particularly in small clinics or practices, paper systems are still simpler and less costly.

Preventive Care Flow Sheets provide screening guidelines with cues for action on a single page in the patient's chart. These flow sheets significantly increase pap smear screening rates as well as other cancer screening procedures.

Studies of preventive services in primary care identified factors that impede or facilitate the integration of these services. The most promising approaches for increasing preventive care are organizational features such as chart flow sheets, feedback about performance, computer-based systems and patient -held mini-records.

In summary, the more effective the communication among the patient, health care provider, and laboratory, the more effective the tracking system in assuring that patients receive the care needed to prevent cervical cancer.

Barriers To Follow-Up

Patients with abnormal screening results, particularly those suggestive of cancer or the presence of Human Papilloma Virus (HPV), are at increased risk for developing invasive cervical cancer. They need to be evaluated and treated with appropriate follow-up care. Approximately 60% of patients with abnormal Pap smears carry through on their health care providers' recommendations for follow-up and treatment (Koss, 1989).

In health care settings that made no special efforts to increase return rates for recommended follow-up care and treatment, patients returned at rates ranging from 20-74% (Lane, 1983). Studies of interventions with aggressive and costly follow-up techniques have achieved rates ranging from 33-95% (Frisch, 1986).

Beliefs

Studies of patient follow-up with recommendations for treatment after an abnormal Pap smear do not explain why women do not return for repeat testing after an abnormal smear. The aim of a study by Paskett et al. (1990) was to understand why women with abnormal Pap smears fail to get the recommended follow-up Pap smear. Issues and beliefs found to significantly affect follow-through included:

- Health care provider's opinion
- Perceived accuracy or seriousness of the result
- Perceived value of early detection
- Familiarity with the procedure
- Time pressures
- Perceived risk of cancer
- Fear of cancer

Recommendations

The following strategies may improve patient follow through on health provider recommendations after an abnormal Pap smear.

- Health care providers should use a tracking system, preferably computerized or at least on paper, that identifies and follows up results of abnormal Pap smears and patient follow-through. This system allows health care providers to determine follow-up rates and to locate patients in need of reminders.
- Efforts should be targeted at two levels. First, information should be offered to patients with abnormal results to address their concerns about test results. Second, facilitating conditions such as cost, transportation, access to colposcopy services, and clinic friendliness should be considered.
- Strategies should be "stepped" to increase cost to health care providers and intensity only with the more recalcitrant patients. Educational materials should be sent to all patients when notified of an abnormality. Patients who do not return for follow-up after abnormal results should receive a phone call from clinic personnel. If patients do not return to the clinic, they should then receive certified letters and/or visits from public health personnel. This strategy first encourages patients through simple, inexpensive, and practical efforts.

Nutritional Aspects of Women's Cancers

Over the last ten years, several studies have reported a "protective" effect of Vitamins A, C, beta (β) -carotene, E, and folacin against cervical cancer and its precursors. In one case-control study investigating nutrient status and invasive cervical cancer using dietary and serologic indicators, the results showed a strong effect of Vitamin C and a lesser effect of carotenoids on reducing the risk of invasive cervical cancer. Preformed Vitamin A and folacin were not related to risk. The authors stated that Vitamin C, as an antioxidant , is essential to the synthesis of collagen, the major component of the extracellular matrix and the body's first barrier against tumor cell invasion. (Herrero et al., 1991 and Potischman et al., 1991).

In a Latin American case-control study, a trend of decreasing risk was also associated with higher levels of β-carotene (Verreault et al., 1989). Higher β-carotene levels have been associated with a multitude of immune responses, including enhanced responses of T and B lymphocytes, cytotoxic T-cell capacities, natural killer cell activity and interleukin-2 receptors. Alpha (α) -carotene has also shown enhanced tumoricidal activity and may function in this role in combination with, or in addition to, β-carotene. β-carotene also has antioxidant capacities that may be relevant to quenching radicals produced during infection or inflammation of the cervix or released during phagocytosis of tumor cells. These studies provide strong support for a protective effect of Vitamin C and β-carotene but little effect from preformed Vitamin A, E and folacin.

A review article of the epidemiologic literature from 1985 to 1993 assessed the relationship between antioxidants and cancer risk (Flagg et al., 1995). After careful examination of five dietary assessments and two serum evaluations, they report the strongest protective effects from Vitamin C and mixed effects from carotenoids and Vitamin E.

The following table summarizes these findings:

Summary of Results for Uterine & Cervical Cancer

Antioxidant	Measure	Studies	Protection (1)	Strength (2)	Dose Response (3)
Carotenoids	Diet	5	2	2	1
	Serum	1	1	1	1
Vitamin C	Diet	5	5	4	2
	Serum	0	0	0	0
Vitamin E	Diet	3	1	1	1
	Serum	2	1	1	0

1. Number of studies demonstrating an inverse association between the specified antioxidant and cervical cancer.
2. Number of studies revealing at least a 50% reduction in risk of cervical cancer with increasing levels of the specified antioxidants.
3. Number of studies demonstrating decreasing risk of cervical cancer across at least 3 levels of the specified antioxidant.

Source: "Epidemiologic Studies of Antioxidants and Cancer in Humans" by Flagg et al. (1995) *Journal of the American College of Nutrition*, *14:* 419-427.

One of the problems in nutritional epidemiology research is that certain foods contain a number of potentially beneficial components. Determining which components provide the most significant contribution is the challenge. It is possible that nutrients or phytochemicals other than carotenoids or Vitamin C are responsible for reducing the risk of lung, upper aerodigestive tract, or cervical cancers (Potischman et al., 1993). The only way to demonstrate definitive cancer prevention through antioxidant consumption may be through randomized clinical trials.

Potischman reported that the majority of serologic and dietary studies indicate no relation between Vitamin A and cervical neoplasia (Potischman, 1993). Her conclusions indicated that dietary carotenoids are important at all stages of cervical neoplasia, but these studies were not consistent. The majority of studies showed that higher levels of dietary and serologic Vitamin C were associated with reduced risk for all stages of cervical neoplasia. Two of the serologic studies reported lower Vitamin E levels with higher grade cervical lesions. Women with invasive cancers had even lower concentrations of Vitamin E than those with dysplasia. However, more data is required to support this protective effect. Folate also appeared to be important in the studies of cervical dysplasia more so than in studies looking at advanced lesions. The author concluded her review of folate by stating that further work is needed to evaluate this nutrient across all grades of preinvasive cervical disease.

University of Arizona Cancer Center researchers investigated the role of folic acid supplementation on the natural history of cervical intraepithelial neoplasia (Childers et al., 1995). They concluded that daily supplementation with 5 mg. of folic acid does not enhance the regression of early epithelial abnormalities of the cervix. The question remains whether correction of folate deficiency, prior to epithelial changes, could influence the outcome.

The above cited studies offer information on the nature of the investigations in micronutrient impact on cervical epithelial abnormalities. The studies indicate how difficult it is to isolate and attribute effects to any particular micronutrient. Experts conclude that nutrition is an important component from which health and disease arise. Continued research in this area is critical to cancer control efforts.

Dietary Sources of Vitamins

- Dietary sources of carotenoids are dark-green, leafy vegetables and yellow, red and orange fruits and vegetables.
- Dietary sources of Vitamin C include citrus fruits, dark-green leafy vegetables, tomatoes and potatoes.
- Dietary sources of Vitamin E include vegetable oils (the richest source), whole grains, wheat germ, nuts and seeds.

Human Papilloma Virus and Risk of Cervical Invasive Neoplasia

Human Papilloma Virus (HPV) has been implicated in the etiology of cervical dysplasia leading to cancer *in situ*, cervical intraepithelial neoplasia and invasive cervical neoplasm. Reports indicate that HPV is diagnosed in 93% of all cervical neoplasms (Schiffman, 1993). These findings are important in the triage and management of cervical dysplasia.

HPV comprises a family of viruses that includes more than 60 viral types (International Agency for Research on Cancer, 1995). These viruses are known to cause warts at diverse sites. About 20 viruses infect the genital area. Genital HPV infection may involve large areas of urogenital, perineal, perianal, and anal epithelium. In men, a common site of genital warts is the base of the shaft of the penis, a site that is not easily covered by a condom. Therefore, even consistent and correct use of condoms may not protect against transmission of genital HPV.

Given the high prevalence of HPV infection relative to the incidence of cervical cancer, HPV alone is not capable of inducing cervical cancer. Exposure to other factors, called "cofactors," is important in the development of disease. Possible "cofactors" include smoking, oral contraceptive use, diet, parity and sexually transmitted diseases. Other host factors include immunologic compromised states, with those infected with HIV at higher risk (IARC, 1995).

Younger, rather than older, women are more likely to have HPV DNA detected in genital tract specimens. HPV DNA is rarely detected in genital tract specimens of women who report no previous sexual activity. These findings help target those at higher risk for being HPV infected.

The typical epidemiologic profile of women with cervical intraepithelial neoplasia includes: women with more sex partners, more cigarette smoking, earlier ages at first sexual intercourse, and lower socioeconomic status (Schiffman, 1993). HPV infection was associated with over 76% of cervical cancer cases. An association of parity with risk of CIN was observed in both HPV negative and HPV positive cases. The authors concluded that the majority of all grades of CIN can be attributed to cancer-associated types of HPV infection. The natural history of HPV has **preventive,** as well as **etiologic** importance.

Natural History

- Although most individuals with genital HPV infection do not develop signs or symptoms brought to the attention of the health care provider, it is likely many infections cause microscopic intraepithelial lesions that are never detected.
- Within a few years of initial infection, the molecular, microscopic and clinical signs of the initial infection are no longer present in most individuals.
- Severely impaired cell-mediated immunity appears to enhance replication of the virus, thereby increasing the probability of an individual developing new or recurrent lesions.
- Only a small percentage of individuals infected with an oncogenic type of HPV develop cancer.
- Cervical cancer is a common HPV-associated malignancy, perhaps in part because cells capable of proliferation at the junction of columnar and squamous epithelium are exposed to the surface and are therefore, most susceptible to infection and transformation by HPV.

Vaccination

A **therapeutic** vaccination is currently being tested to treat patients with established HPV-associated precancer or cancer. **Prophylactic** vaccination may potentially protect against HPV infection. Theoretically, protection can be achieved by induction of virus-neutralizing antibodies prior to exposure. Successful therapeutic vaccination depends on stimulation of cellular immune response. Efforts are currently being made to develop and test a safe vaccine to prevent the development and spread of infection.