

Rise in Tonsillar Cancer Parallels HPV Positivity

BY NEIL OSTERWEIL
Contributing Writer

CHICAGO — A twofold to threefold increase in the incidence of tonsillar cancer over several decades was paralleled by a similar rise in the incidence of tumors positive for the human papillomavirus, the results of a Swedish cohort study indicate.

At the same time, however, survival rates among patients with tonsillar cancer also increased, possibly because of the higher proportion of HPV-positive cancers, which tend to have a much better prognosis than other oral cancers, Dr. Hanna Dahlstrand said at the annual meeting of the American Society of Clinical Oncology.

The reasons for the increase in HPV-positive tumors are not known, although they could be related to a possible increase in sexual behaviors, particularly in urban centers, Dr. Dahlstrand said.

Although Sweden is a relatively small nation, the results may be applicable to other countries, she noted. In the United States, for example, the incidence of HPV-related oropharyngeal squamous cell carcinomas has increased since 1973, while the incidence of squamous cell carcinomas at other oral sites has either remained constant or declined. In Finland, the incidence of tonsillar cancers doubled from 1956 through 2000, said Dr. Dahlstrand of the department of oncology-pathology at the Karolinska Institute in Stockholm.

HPV DNA has been shown to be present in 40%-75% of oropharyngeal cancers, compared with about 25% of all head and neck cancers.

"It is only the high-risk types of HPV that are found, with at least 90% dominance of HPV-16, and the oncogenes on HPV, E6 and E7 are transcribed," she said, "And impor-

tantly, there is a temporal connection: Exposure to HPV-16 precedes by at least 9 years the diagnosis, and has been shown to be a strong risk factor for tumor development."

HPV-positive oropharyngeal cancers tend to occur more often among nonsmokers and younger patients. Risk factors include multiple sexual partners, younger age at first intercourse, and oral sex. Several studies have shown that the presence of HPV positivity is associated with about a 50% reduction in 5-year mortality, Dr. Dahlstrand noted.

She and her colleagues at the Karolinska Institute conducted a nationwide cohort study using the exhaustive clinical and demographic databases available to Swedish investigators. Their goals were to see whether there has been an increase in the incidence of tonsillar cancer in Sweden; to determine whether such an increase, if present, could be linked to the proportion of HPV-positive tumors; and to see whether the incidence of HPV-positive tonsillar cancers would have an effect on survival.

They identified a total of 2,165 incident cases of tonsillar squamous cell carcinoma from 1960 through 2003, using the Swedish National Cancer Registry.

To determine survival, the investigators used records from the Swedish Causes of Death Register, and checked them against the Swedish Emigration Registry from 1960 to 2001 to ensure that cohort members were not lost to follow-up. They identified a total of 1,800 survivors as of 2003.

The investigators also assessed the incidence of tonsillar cancer from 1970 to 2001 and survival in a Stockholm cohort, and used this cohort to control for treatment, tumor-nodes-metastasis stage, and cause of death. They identified 515 cases in this cohort, and 337 survivors as of 2001.

They were able to obtain 203 biopsy samples and screened them for HPV using polymerase chain reaction testing; they then typed and sequenced the HPV to determine expression of the E6 and E7 oncogenes and expression of HPV-16.

In the nationwide cohort, there was a twofold increase in the incidence of tonsillar cancers, from 1.2/100,000 population to 2.4/100,000, from 1960 to 2003. There was no parallel increase in cancers of the oral cavity (for example, mobile tongue or floor of the mouth), however.

In the Stockholm cohort, tonsillar cancers increased from 1.3/100,000 to 3.6/100,000, or 2.8-fold, from 1970 to 2002. There was also a 2.9-fold increase in the proportion of HPV-positive tonsillar cancers during that same time period. This increase became significant for the 1990-1999 period, compared with 1970-1979, and remained significant for 2000-2002. During the 1970s, 23% of cases were HPV positive, which increased to 28% in the 1980s, 57% in the 1990s, and to 68% into the 21st century.

The mean 5-year relative survival rate among men with tonsillar cancer also increased in Sweden since the 1960s, from 32% to 53% in 1990-2001. In the Stockholm cohort, in a Cox multivariate analysis adjusted for age, gender, stage, and treatment, the investigators found a similar significant increase in relative 5-year survival, with a relative hazard ratio of 0.54 for 1990-2001, compared with 1970-1979. The presence of a lower proportion of stage I and II tumors in the 1990s, compared with the 1970s, suggests that the improvement in survival over the years cannot be explained by earlier diagnosis, Dr. Dahlstrand said.

Dr. Dahlstrand stated that she had no relevant financial disclosures. ■

Consider Epstein-Barr In Genital Ulceration

DESTIN, FLA. — Since Epstein-Barr virus is known in rare cases to initially present as severe, painful genital ulcerations without other clinical or laboratory evidence of acute disease, this infection should be considered in the differential diagnosis of patients who present with such lesions.

"You won't see it presenting this way very often, but . . . if you have young patients presenting like this, remember to test for EBV," Dr. Bari Cunningham said at a meeting sponsored by the Alabama Dermatology Society.

Dr. Cunningham, of the University of California, San Diego, described the case of a 15-year-old girl who presented with extremely painful vaginal lesions.

"Of course, sexually transmitted diseases were first and foremost on everybody's mind," she said, noting that the patient, who was adamant that she was not sexually active, was traumatized by the constant questioning about her sexual history and by the fact that no one believed her.

When the cultures came back negative, the differential was broadened, and Behçet's syndrome, systemic lupus erythematosus, pyoderma gangrenosum, and inflammatory bowel disease were among the diagnoses considered. The girl's condition worsened. She became sicker and stopped eating, and more skin surfaces became involved. She was noted to have a swollen liver.

All cultures up to that point were negative and a complete blood count was unremarkable; however, mild elevations on liver function tests, which developed during hospitalization, were noted, and the test for EBV immunoglobulin M came back positive.

Several cases of EBV presenting in this manner have been reported in the literature, Dr. Cunningham said.

—Sharon Worcester

Expert Argues for Universal HPV Vaccination

BY DOUG BRUNK
San Diego Bureau

CALGARY, ALTA. — As an epidemiologist whose research focuses on the prevention of cervical cancer, Dr. Eduardo L. Franco spends a lot of time arguing with health care professionals and patients who say that more research is needed before universal human papillomavirus vaccination can be recommended worldwide.

"Although clinical experience has just passed 6 years, the evidence base is one of the strongest in disease prevention," Dr. Franco said at the annual meeting of the Society of Obstetricians and Gynaecologists of Canada. "The standard of proof is far more rigorous than that used in the evaluation of candidate vaccines of the past."

Dr. Franco, director of the division of cancer epidemiology at McGill University, Montreal, shared several examples of arguments against HPV vaccination that he encounters, followed by his counterargument for each.

One chief argument he hears is that the vaccine is too costly and unaffordable where it's most needed. However, he said, procurement programs such as the Centers for Disease Control and Prevention's Vaccines for Children Program and the Pan American Health Organization's revolving fund should help to lower the cost. "Historically," he added, "prices decline with time since deployment."

In addition, ongoing studies of simplified schedules—such as administering two doses instead of three—may affect price. Other common arguments against HPV vaccination include the following:

► **There are no data on long-term duration of protection.** In fact, to date, studies demonstrate a sustained antibody response with no indication that humoral im-

munity will wane before 10 years. "Even with lowered antibody titers, postvaccination protection has continued unabated," said Dr. Franco, who also is a professor of epidemiology and oncology at McGill.

► **Protection is limited; vaccines cover only two oncogenic types.** In fact, protection is against the two most important types (HPV 16 and 18), which translates into a protective fraction of 70% of all cervical cancers that "is likely to be expanded via cross-protection," he said.

► **Screening will continue to be needed.** True, Dr. Franco said, but recent progress on new technologies such as HPV testing with Pap triage "will permit extending screening intervals safely and cost effectively."

► **There is a risk of type replacement, which occurred with the pneumococcal vaccine.**

Type replacement is unlikely to occur because there is no epidemiologic proof that HPV types compete for specific niches. "Several studies have tested this hypothesis," he noted.

► **We should not vaccinate preteens and teens; there are no efficacy data on patients aged 9-14 years.** "Immunobridging" studies

'Even with lowered antibody titers, postvaccination protection has continued unabated.'

DR. FRANCO

show that vaccine-induced humoral response in preteens is the highest among all groups, "which is sufficient justification for expectation of benefit," he said.

► **There is no proof yet that vaccination can reduce the risk of invasive cancers.** Dr. Franco counters this notion by pointing out that absence of evidence is not evidence of absence.

Dr. Franco disclosed that his entire research program has been funded by the Canadian Institutes of Health Research (CIHR), the National Cancer Institute of Canada, and the National Institutes of Health. He has served as an occasional adviser to several companies with products related to cervical cancer prevention. ■

