CORRESPONDENCE

Nonmelanomatous Skin Cancer Following Cervical, Vaginal, and Vulvar Neoplasms: Etiologic Association

Human papillomavirus infection is the major cause of cancers of the cervix, vagina, and vulva *(1)*. Nonmelanomatous skin cancers have been associated with human papillomavirus infection in patients with epidermodysplasia verruciformis and in patients who are immunosuppressed or nonimmunosuppressed, although the data are scant *(1,2)*.

We used the cancer registry of the Swiss Canton of Vaud (with a population of approximately 600 000 in 1990) for the period from 1974 through 1994 to obtain additional quantitative information on this topic, which has pathogenic and public health implications. Data were collected for women who had *in situ* or invasive neoplasms of the cervix, vagina, or vulva and for women who had nonmelanomatous skin cancer. These data were then used to calculate the incidence of nonmelanomatous skin cancer in women who had been registered with an *in situ* or invasive neoplasm of the cervix, vagina, or vulva *(3)*.

The registry is tumor based, and multiple primary tumors in the same person are entered separately. The basic information available consists of sociodemographic characteristics of the patient, the primary site of the tumor, the histologic type of the tumor according to the standard International Classification of Diseases (ICD) for Oncology *(4)*, and the time of diagnostic confirmation. Passive and active follow-ups are recorded, and each subsequent item of information concerning a registered cancer is used to complete the record of that patient.

Since 1974, a registration scheme that applies the standardized rules used for incident cancers has been used for carcinoma *in situ* and severe dysplasia (CIN III, cervical intraepithelial neoplasia III) of the uterine cervix (ICD code: 180.0–180.9), vagina (ICD: 184.0), and vulva (ICD: 184.1–184.3) *(4)*.

In the present study, when all synchronous neoplasms were excluded, there were 2339 histologically confirmed cases of carcinoma *in situ* of the cervix uteri, nine cases of carcinoma *in situ* of the vagina, and 85 cases of carcinoma *in situ* of the vulva. The study also included 789 cases of invasive neoplasms of the cervix, 69 cases of invasive neoplasms of the vagina, and 153 cases of invasive neoplasms of the vulva. These cases were followed to the end of 1996 for the occurrence of cancer, migration, or death.

We calculated the expected numbers of individuals with nonmelanomatous skin cancer based on site-, age-, and calendar-period-specific incidence rates, multiplied by the observed number of person-years at risk. The statistical significance of the observed/expected ratios (standardized incidence ratio [SIR]) and the corresponding 95% confidence interval (CI) were based on the Poisson distribution.

Table 1 gives the observed and expected numbers of nonmelanomatous skin neoplasms after diagnosis of *in situ* or invasive neoplasms of the cervix, vagina, and vulva. A statistically significant excess of skin cancer was registered after cervical neoplasms (44 observed and 24 expected; SIR = 1.8; 95% CI = 1.3–2.5) and vulvar neoplasms (13 observed and four expected; SIR = 3.2; 95% CI = 1.7–5.5). Likewise, three nonmelanomatous skin cancers were observed after vaginal neoplasms versus one expected (SIR = 2.9; 95% CI = 0.6–8.6). Overall, 60 skin cancers were observed versus 29 expected (SIR = 2.1; 95% CI = 1.6–2.7).

Table 1. Observed and expected cases, in Vaud, Switzerland, from 1974 through 1994, and standardized incidence ratios (SIRs) of subsequent nonmelanomatous skin cancer after an initial diagnosis of *in situ* or invasive neoplasms of the cervix, vagina, and vulva, as well as the corresponding 95% confidence intervals (CIs)

Site of *in situ* or invasive primary tumor	No. of nonmelanomatous skin cancers		SIR (95% CI)
	Observed	Expected	
Cervix (n = 3128)	44	24	1.8 (1.3–2.5)
Vagina (n = 78)	3	1	2.9 (0.6–8.6)
Vulva (n = 238)	13	4	3.2 (1.7–5.5)
Total (n = 3444)	60	29	2.1 (1.6–2.7)

An excess of nonmelanomatous skin cancer after diagnosis of carcinoma *in situ* of the cervix has been reported *(5,6)*. The present data extend this observation to other neoplasms of the lower female genital tract and, therefore, provide epidemiologic support to the suggestion of a possible role of human papillomavirus infection in the etiology of nonmelanomatous skin cancer *(7)*.

FABIO LEVI
LALAO RANDIMBISON
CARLO LA VECCHIA

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NOTES

Affiliations of authors: F. Levi, L. Randimbison, Registre Vaudois des Tumeurs, Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland; C. La Vecchia Istituto di Ricerche Farmacologiche ''Mario Negri,'' and Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Italy.

Correspondence to: Fabio Levi, Registre Vaudois des Tumeurs, CHUV-Falaises 1, CH-1011 Lausanne, Switzerland (e-mail: fabio.levi@inst.hospvd.ch).

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Re: Distinguishing Second Primary Tumors From Lung Metastases in Patients With Head and Neck Squamous Cell Carcinoma

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The recent paper by Leong et al. *(1)* highlights progress regarding a long-standing oncology dilemma in distinguishing a solitary metastatic deposit from a new cancer in patients with known prior cancer. The specific clinical scenario is familiar to those who frequent head and neck tumor boards—specifically, the patient with known head and neck cancer (squamous cell carcinoma) who simultaneously or subsequently manifests a solitary pulmonary nodule, which is similarly confirmed as squamous cell carcinoma.

Many head and neck oncologists have turned wistfully toward their tumor board pathologist with the simple question, ''Is this a metastasis or a new primary tumor?'' The promise of this published work by Leong et al. *(1)* is that we are moving closer to providing the clinician with molecular diagnostic tools to answer the question more precisely.

Judicious application of molecular techniques to complement clinical judgment in the ''metastasis versus primary tumor'' scenario will clearly prove beneficial in selected circumstances. Nevertheless, maximizing clinical thinking before soliciting molecular ''truth telling'' will be important. In their abstract, Leong et al. state ''. . . a solitary SCC [squamous cell carcinoma] in the lung more likely represents a metastasis than an independent lung cancer.'' However, this is largely dependent on the patient cohort selected. The study group in the paper by Leong et al. is dominated by patients with advanced, lymph node-positive, and/or recurrent head and neck cancers. Of the 16 patients studied, 13 presented with stage IV tumors and 15 were lymph node positive at presentation. These represent compelling prognostic features for locoregional disease recurrence and eventual distant metastases. Thus, it is not surprising that 12 of 16 lung tumors appeared to represent metastases in this group of patients with highly advanced-stage disease for whom clinical judgment would largely dictate the same. This is by no means meant to detract from the importance of this work. Rather, it is suggested that such molecular analysis may prove far more important in patients with earlier stage disease for whom the clinical likelihood of distant metastasis is deemed far lower.

Approximately one quarter to one third of the patients with head and neck cancer present with stage I or stage II disease (lymph node negative); in these patients, lung metastases would be distinctly unusual. For these patients, the cost of mistakenly assuming a metastatic process could be tragic, and the value of confirming a molecular distinction may be critical to optimizing therapy recommendations.

Leong et al. state in the ''Discussion'' section, ''Most solitary lung nodules in patients with HNSCC [head and neck squamous cell carcinoma] may actually reflect advanced tumor spread.'' These authors would not wish to inadvertently mislead the general oncologist into thinking that this is true for all patients with head and neck cancer. This conclusion is strongly influenced by the clinical staging of the original tumors. A molecular examination of 16 patients with early stage head and neck tumors who manifest solitary pulmonary nodules might well lead others to draw the opposite conclusion. Nevertheless, these advances in tumor fingerprinting will surely provide tangible benefits to selected cancer patients in whom the judicious application of molecular data will complement and clarify clinical judgment.

PAUL M. HARARI

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Correspondence to: Paul M. Harari, M.D., Department of Human Oncology, 600 Highland Ave. K4/B100, Madison, WI 53792-0600.

RESPONSE

We welcome Dr. Harari's refreshing embrace of a novel strategy for the resolution of a long-standing oncologic impasse. Comparative microsatellite analysis is a highly effective tool in distinguishing second lung tumors from lung metastasis. No doubt, similar genetic strategies addressing equally relevant clinical issues will play an increasing role in the integrated multidisciplinary approach to patients with head and neck squamous cell carcinoma (HNSCC) and cancers at other sites.

As always, caution and discretion must be exercised when generalizing study results to the individual patient. Our study reflects the experience of a large tertiary care center where patients are often referred for management of advanced HNSCC. As Dr. Harari points out, the incidence of solitary lung metastases will probably be lower in patient populations over represented by low-stage HNSCCs. For the individual patient with HNSCC, however, microsatellite analysis remains a valid and valuable tool for discerning the nature of a solitary lung tumor. The use of such molecular approaches is not intended to replace sound clinical judgment but to facilitate it.

WILLIAM H. WESTRA
WAYNE M. KOCH
DAVID SIDRANSKY
JIN JEN

NOTES

Affiliations of authors: W. H. Westra (Department of Otolaryngology–Head and Neck Surgery and Pathology), W. M. Koch, D. Sidransky, J. Jen (Department of Otolaryngology–Head and Neck Surgery), The Johns Hopkins Medical Institutions, Baltimore, MD.

Correspondence to: William H. Westra, M.D., The Johns Hopkins Medical Institutions, Department of Pathology, 600 N. Wolfe St., Baltimore, MD 21287-6417.