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A deficit in biopsying potentially premalignant oral lesions in Puerto Rico

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Abstract

The study findings suggest that there is a substantial shortfall in the biopsying of potentially precancerous oral lesions in Puerto Rico. Persons living in Puerto Rico who have intraoral lesions suspicious for oral cancer or precancer are most likely to be biopsied only after developing an invasive cancer and therefore are not receiving the benefits of early detection.

Introduction

Worldwide in 2002, there were an estimated 274,000 new cases of and 127,000 deaths attributed to oral cancer (1). Age-adjusted oral cancer incidence and mortality rates for Puerto Rico (PR) are among the highest in the Western Hemisphere, particularly among males (2).

Most oral cancers are squamous cell carcinomas, which almost always arise from red and/or white precursor lesions presenting on the surface mucosa (3,4). Although it is generally agreed that such lesions should be biopsied and evaluated histopathologically (5–8), oral precancers and early cancers are often asymptomatic and can go undetected in the absence of a careful oral examination. In addition, even identified suspicious lesions can be ignored by persons who have them or by healthcare practitioners. While most potentially precancerous intraoral lesions do not transform to invasive cancer, those that do will almost always be identified, often at more advanced, symptomatic stages.

In most general populations, the identification and biopsying of all suspicious oral mucosal lesions would be expected to yield a spectrum of histopathologic diagnoses reflecting benign, potentially precancerous, and malignant conditions, with cancers comprising only a small

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proportion of biopsied lesions (6,9,10). If in a general population, the fraction of oral biopsies diagnosed with invasive oral cancer is high, such a distribution could indicate an inadequate identification and removal of suspect lesions.

Because oral cancer incidence rates are elevated in PR, one would expect a concomitantly high occurrence of precancerous oral lesions. However, in a previous, informal review of pathology reports generated by pathology laboratories in PR during 2003, we identified a high frequency of oral biopsy specimens diagnosed with invasive oral cancer (almost all of which were squamous cell carcinomas), but comparatively few specimens diagnosed with benign or potentially precancerous diagnoses.

Based upon those observations, we sought to more formally evaluate whether the relative frequency of oral cancer (i.e., the frequency of persons diagnosed with an oral cancer relative to the frequency of persons with histopathologic diagnoses that would have appeared clinically suspicious for oral cancer or precancer at the time of biopsy) is disproportionately high in PR. In order to assess whether the observed relative frequency of oral cancer is inordinately high in PR, we contrasted the relative frequency of oral cancer in PR pathology laboratories with the analogous oral cancer relative frequency observed in New York City (NYC) pathology laboratories. Because oral premalignant lesions of the surface mucosa are associated with the development of oral squamous cell carcinoma (OSCC), all non-squamous cell carcinomas were excluded from our primary study analysis.

If our initial observation was correct regarding the high proportion of oral cancer diagnoses in PR pathology laboratories, our current analysis would be expected to reveal a relative frequency of oral cancer that is notably higher in PR relative to NYC pathology laboratories. Such a finding would provide strong evidence that early suspect lesions are not receiving adequate attention in PR in terms of identification and biopsy.

Materials and Methods

Nine pathology laboratories were selected for and participated in the study, seven in PR and two in NYC. Of the seven PR pathology laboratories, six were general pathology laboratories and one specialized in oral tissues; these seven laboratories see a large percentage of the oral biopsies in PR. In NYC, one general (Bellevue Hospital) and one oral pathology laboratory (New York University College of Dentistry, NYUCD) were included for comparative purposes.

All pathology reports generated during 1/2004–5/2005 by the above pathology laboratories were reviewed if they indicated a soft tissue biopsy from an eligible intraoral site. Eligible topographical sites included the tongue, gingiva, floor of mouth, palate, as well as other and unspecified parts of the mouth (International Classification of Diseases for Oncology, 3rd revision (11), C01–C06); i.e., anatomical sites easily examined by health care practitioners. Excluded sites included the lips, major salivary glands, tonsils, and oropharynx (C00, C07–C10).

Histopathologic diagnoses involving oral soft tissues were hierarchically categorized as a) invasive oral cancer, b) epithelial dysplasia (including carcinoma *in situ*), c) hyperkeratosis and/or epithelial hyperplasia (HK/EH), or d) any other oral soft tissue pathosis. Table 1 presents the oral soft tissue diagnoses observed and the category into which the various diagnoses were placed. The analysis was restricted to persons whose diagnosis fell into one of the first three categories and in the primary analysis, to cancer cases with invasive OSCC.

Each person receiving at least one oral biopsy during the 17-month period of observation was assigned one diagnosis based upon the above diagnostic categories. When a person received

one or more biopsy and the histopathologic diagnosis included diagnoses falling under more than one diagnostic category, only the most severe category was included. The exception to the above rule was in those rare instances in which an individual received sequential biopsies from the same anatomical site over six months or more, and the biopsies revealed a progression in the histopathology of the lesion from one hierarchical category to a higher category (e.g., from dysplasia to invasive cancer). In those instances, only the lesser diagnosis was included, based upon the premise that the person had been identified with a lesser category of disease and was being followed.

The relative frequency of invasive oral cancer was defined as the number of individuals with an invasive OSCC divided by the total number of persons diagnosed histologically with an OSCC, epithelial dysplasia, or HK/EH. This denominator was used because lesions with these diagnoses would likely have appeared as clinically suspicious for oral cancer or precancer at the time of biopsy. Both crude and age/gender-stratified relative frequencies were estimated for the pathology laboratories located in PR (all laboratories combined and separately for general and oral laboratories), Bellevue Hospital, and NYUCD.

Chi-square or Fisher's Exact tests were used to test the statistical significance of differences in proportions. Human Subjects Committee approval was obtained prior to study initiation.

Results

Figure 1 presents the relative frequency of invasive oral cancer as defined above. In the PR pathology laboratories, 66.9% (87/130) of persons biopsied with a lesion clinically suspicious for oral cancer or precancer were histopathologically diagnosed with an invasive cancer. The analogous percentages were 39.7% (23/58) and 4.3% (13/300) in the Bellevue and NYUCD pathology laboratories, respectively. Therefore, the relative frequency of oral cancer was notably higher in PR than in either of the NYC laboratories, and the respective differences were statistically significant (each comparison, $p < 0.001$).

Analyses were also conducted after stratifying on pathology laboratory type (oral or general). When the relative frequency of oral cancer was compared across the PR and Bellevue general pathology laboratories, the proportion of oral cancers was clinically and statistically significantly higher in the PR general pathology laboratories (73%, 77/105) than at Bellevue (40%, 23/58) ($p < 0.001$). In the oral pathology laboratory in PR, the relative frequency of oral cancer was also clinically and statistically significantly higher than in the NYUCD laboratory [40% (10/25) vs. 4% (13/300); $p < 0.001$].

Table 2 presents the relative frequency of oral cancer for the participating pathology laboratories after further stratification on age and gender. When all PR laboratories were aggregated (general + oral), the relative frequency of oral cancer was lower in younger than older females (23% vs. 66%; $p = 0.002$), but high in magnitude for both younger and older males (78% vs. 82%). When age-, gender-specific oral cancer relative frequencies were compared across PR and NYC separately for general and oral pathology laboratories, the relative frequencies were always higher in PR, but the differences consistently statistically significant for males only.

Twelve females and 12 males diagnosed through NYUCD were excluded from the age/gender comparisons due to missing age data; one male had oral cancer. One 44-year old with HK was excluded from the Bellevue group due to missing gender data. When these individuals were reintroduced into the age/gender-specific PR-NYUCD and PR-Bellevue analyses using all possible age/gender distributions, differences in statistical significance/non-significance remained unchanged.

In addition to the primary analysis, we conducted a parallel analysis of oral cancer relative frequency in which we included oral cancer cases with either a squamous cell or non-squamous cell cancer. The results were similar to those described above, with overall oral cancer relative frequencies for PR, Bellevue, and NYUCD being 69%, 43%, and 5%, respectively (each comparison, $p < 0.001$).

Discussion

The current study sought to formally investigate an initial observation that revealed a higher than expected percentage of invasive cancers among oral biopsy specimens diagnosed in PR pathology laboratories relative to that expected in the United States (US). Such a finding is important because it suggested a deficit in the biopsying of oral lesions suspicious for precancer and very early (non-invasive) cancer in PR, a deficit that could have important implications in terms of oral cancer morbidity and mortality.

In the current investigation, we compared the relative frequency of invasive oral cancer in PR pathology laboratories to the analogous relative frequencies observed in two NYC pathology laboratories. The purpose in selecting the two NYC laboratories, both of which serve populations high in racial and ethnic diversity, was to provide comparative points of reference by which we could evaluate whether the relative frequencies of oral cancer observed in the PR pathology laboratories were low, intermediate, or high. Because observed differences in the crude relative frequencies could be confounded by age, gender, and pathology laboratory type, we stratified our data on those variables. We did not further stratify on race/ethnicity, however, because our purpose was not to determine whether Hispanics are more or less likely to receive a biopsy than other ethnic groups, but rather, to determine whether biopsy patterns were different for the populations served by the PR and NYC pathology laboratories.

In the current pathology laboratory comparisons, we found that the overall relative frequency of oral cancer diagnoses in the PR pathology laboratories was significantly higher, both clinically and statistically, than the percentages identified in each of the two NYC laboratories. Previous studies of individuals biopsied with either oral leukoplakia or suspicious oral lesions in general have also reported relative frequencies of oral cancer that were markedly lower than those seen in PR. In an investigation based upon oral screenings involving over 23,000 Minnesotans, 12.5% of lesions deemed suspicious enough for biopsy contained oral cancer (12) while a study that reviewed all oral pathology reports generated in Northern Ireland during 1975–1994 reported that 36% of persons whose histopathologic diagnosis suggested a lesion clinically suspicious for oral cancer were diagnosed with an oral squamous cell carcinoma (13). More recently, it was reported that 12.9% of oral leukoplakia cases biopsied by a Taiwanese university oral surgery department were histopathologically diagnosed with invasive oral cancer (6).

Oral pathology laboratories generally receive biopsy specimens from dentists and dental specialists, and there is evidence that dentists are more likely to biopsy asymptomatic oral lesions than their medical counterparts (14). Consequently, because oral premalignant lesions tend to be asymptomatic, it is reasonable to expect that the relative frequency of oral cancer would be *lower* in oral, relative to general, pathology laboratories. This, in fact, was observed in both PR and NYC; however, in keeping with our other findings, the relative frequency of oral cancer was over nine-times higher in the oral pathology laboratory located in PR (40.0%) than at NYUCD (4.3%). When we further compared the relative frequency of oral cancer in PR general pathology laboratories to that of an NYC public hospital (Bellevue), the relative frequency was 85% higher in PR [73.3% vs. 39.7%, i.e., $(0.733 - 0.397)/0.397$]. Therefore, our analyses indicate that even after taking into account the type of pathology laboratory in which

the biopsy specimens were diagnosed, persons with suspicious oral lesions biopsied in PR were more likely than persons biopsied in NYC to have already developed an invasive oral cancer.

When the effects of age and gender were considered by pathology laboratory type (general/oral), oral cancer relative frequencies for females were higher in PR than in NYC, but the differences were not always statistically significant, a finding that likely reflects the small numbers of females with eligible diagnoses in PR and NYC. On the other hand, oral cancer relative frequencies for younger and older males alike were consistently higher in PR than in NYC, and the differences always statistically significant. Moreover, the relative frequencies for males in PR were inordinately high, often exceeding 80%. In toto, these findings suggest that much of the overall difference in the relative frequency of oral cancer observed between the PR and New York laboratories is explained by the large proportion of PR males with suspicious oral lesions that are biopsied only after developing invasive cancer.

Consistent with our current findings, we previously analyzed oral cancer data from the Central Cancer Registry of Puerto Rico and the US Surveillance Epidemiology and End Results (SEER) program and identified a significant deficit in the proportion of *in situ* cancers in PR relative to the US. The deficit was largely attributable to low percentages of *in situ* diagnoses among PR males and revealed a disparity in the identification of very early (*in situ*) oral cancers in PR relative to the US (15).

Taken together, our findings indicate that in PR, persons, principally males, with intraoral lesions clinically suspicious for oral cancer or precancer are most likely to receive a biopsy only after developing an invasive cancer. Further, the shortfall in the detection and removal of potentially precancerous oral lesions and very early cancers in PR is substantial.

In comparing PR and NYC pathology laboratories, we are not implying that the US represents a strong standard in terms of early oral cancer detection; on the contrary, only one third (33%) of all invasive oral and pharyngeal cancer cases diagnosed during 1996–2002 and registered by SEER were classified as having localized disease (16). Consequently, if biopsying potentially precancerous oral lesions and very early cancers is significantly reduced in PR relative to NYC and the US mainland, such a disparity suggests that the detection of oral pre- and early invasive cancers is particularly problematic in PR.

Delays in diagnosis can have significant ramifications. In the case of premalignant lesions, a biopsy and histopathologic diagnosis is vital in providing information as to how closely a lesion should be followed and whether treatment should be initiated with the intention of preventing malignant transformation. Although the clinical effectiveness of treatments to prevent malignant transformation of precancerous oral lesions has not been evaluated in randomized clinical trials, the management of these lesions, which includes lesion excision, risk factor elimination, and close follow-up, currently offers the best available option to prevent disease progression (17,18).

We did not have information on cancer stage at diagnosis from the participating pathology laboratories and therefore, could not compare the relative frequency of late stage cancers in PR to our comparison sites. However, because oral precancerous lesions and early cancers are more likely to be asymptomatic than late stage cancers, biopsying suspicious asymptomatic intraoral lesions would increase the likelihood of identifying cancers at an early stage. The early diagnosis of invasive oral cancers is important because 5-year survival rates are notably higher for persons diagnosed with localized, relative to regional or metastatic, disease (16, 19). Further, oral cancer patients with early stage disease often require less radical cancer-directed treatment, suffer fewer associated sequelae, and have a better health-related quality of life than cases diagnosed with late stage disease (20,21).

It is unclear why lesions suspicious for oral cancer and precancer tend to be biopsied in PR only after developing an invasive cancer; however, a number of possible explanations exist.

It is possible that some oral cancers may arise from seemingly normal mucosa or from lesions that progress rapidly and are therefore less amenable to clinical identification and biopsy during the premalignant stage (13). These departures from the typically envisioned pathway of oral cancer pathogenesis may explain some portion of the relative frequency of oral cancer diagnoses observed in PR and various other disparate locales. However, in order to account for the disproportionately high relative frequency of oral cancer in PR, the proportion of cancer cases arising via the less clinically detectable pathway would need to be notably higher in PR than in the other geographic areas studied in the current and previous investigations.

Errors in the histopathologic diagnosis of oral specimens represent another possible explanation for the high relative frequency of oral cancer diagnoses in PR. Although the histopathologic diagnosis of oral dysplasia is prone to subjectivity and could lead to some misclassification of disease (22,23), it is unlikely that biopsy specimens are misdiagnosed as invasive cancers at a higher rate in PR relative to the US given the generally striking histologic characteristics of invasive oral cancer.

A more likely explanation for the high relative frequency of oral cancer diagnoses in PR centers on the possibility of patient and/or practitioner delays in diagnosis.

Although the occurrence of patient delays has not been explored in PR, studies conducted in the US suggest that Hispanics seek medical and dental healthcare services less frequently than the general US population (24–27). Moreover, the utilization of cancer-preventive services by Latinos in the US appears to be influenced by a lack of self-efficacy in addressing individual cancer risk factors as well as cultural factors such as “fatalism” or the belief that illnesses, in particular cancer, are God’s will (28). Similar beliefs and practices may present in PR residents and influence their healthcare utilization, thereby leading to delays in receiving biopsies of suspicious oral lesions.

Likewise, the potential for practitioner delays in oral cancer diagnosis has not been investigated in PR. While a number of US studies have explored oral cancer awareness among healthcare practitioners (29), no parallel investigations into oral biopsy practices have been reported for PR, thereby making it difficult to determine how the standard of care on the Island may influence early cancer detection. Further, it is unclear how, whether, or to what extent patient or practitioner delays in oral cancer diagnosis are influenced by the current healthcare system in PR, which includes a managed healthcare plan available to the medically indigent and other qualified individuals. The plan, PR Healthcare Reform, was initiated in the mid-1990s, provides relatively low capitation rates and does not allow healthcare practitioners to charge additional fees for special procedures (30–33).

Our findings provide evidence of a significant disparity in the biopsying of potentially precancerous oral lesions in PR relative to NYC and suggest that PR residents with intraoral lesions suspicious for oral cancer or precancer are most likely to be biopsied only after developing an invasive cancer. The burden appears to be greater among males than females. These findings are important because they imply that many PR residents with oral premalignant lesions are not getting diagnosed in a timely manner and consequently, not receiving the benefits of early detection. In order to reduce the apparent deficit in the early identification and biopsying of suspect oral lesions in PR, it is imperative that the causative factors for the shortfall be determined and addressed.

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Figure 1. The percentage of persons diagnosed with an oral cancer among persons biopsied and diagnosed with either an oral cancer, dysplasia, or hyperkeratosis/epithelial hyperplasia (HK/EH) Percentages above are based on the following proportions: PR (87/130), Bellevue (23/58), NYUCD (13/300).

The percentages of persons diagnosed with cancer were statistically different between PR and both Bellevue and NYUCD; each comparison, $p < 0.001$.

Table 1
Histopathologic diagnoses assigned under the study diagnostic categories.

<u>Invasive cancers</u>
Squamous cell carcinoma
Adenocarcinoma ¹
Adenosquamous carcinoma ¹
Mucoepidermoid carcinoma ¹
<u>Dysplasia</u>
Dysplasia, mild, moderate severe, including <i>in situ</i> carcinoma
<u>Hyperkeratosis and/or epithelial hyperplasia</u>
Hyperkeratosis
Hyperparakeratosis
Hyperorthokeratosis
Epithelial hyperplasia (acanthosis)
<u>Other soft tissue pathoses</u> ²
Mucocoele
Fibroma
Papilloma
Hemangioma
Amalgam tattoo
Fibrolipoma
Amyloidosis
Neurilemmoma
Actinomyces granules
Condyloma acuminata
Lichen planus
Cysts
Granuloma
Periodontitis
Mucositis
Hyperplasia (except epithelial hyperplasia)
Inflammation
Sialadenitis
Pleomorphic adenoma
Candidiasis

¹ Excluded from the primary analysis

² Excluded from all analyses

Table 2
The relative frequency (%) of oral cancer¹ by age and sex in PR and NYC pathology laboratories

PR		Females		Males	
Age (years)	%	n ¹	%	n ¹	
<u>- General & Oral Pathology Laboratories combined</u>					
≤60	22.7 ^{a,c}	5/22	78.3 ^{i,k}	36/46	
61+	65.5 ^{b,d}	19/29	81.8 ^{j,l}	27/33	
<u>- General Pathology Laboratories only</u>					
≤60	25.0 ^e	4/16	87.2 ^m	34/39	
61+	70.0 ^f	14/20	83.3 ⁿ	25/30	
<u>- Oral Pathology Laboratory only</u>					
≤60	16.7 ^g	1/6	28.6 ^o	2/7	
61+	55.6 ^h	5/9	66.7 ^p	2/3	
Bellevue²					
Age (years)					
≤60	15.4 ^{a,e}	2/13	47.8 ^{i,m}	11/23	
61+	57.1 ^{b,f}	4/7	42.9 ^{j,n}	6/14	
NYUCD³					
Age (years)					
≤60	2.9 ^{c,g}	2/69	2.5 ^{k,o}	3/122	
61+	13.6 ^{d,h}	6/44	2.4 ^{l,p}	1/41	

¹ Number of persons with an OSCC/(persons with an OSCC + persons with OED + persons with HK/EH).

² One 44-year old with HK was excluded from the Bellevue group due to missing gender data.

³ Twelve females (no cancers) and twelve males (1 cancer) were excluded from the NYUCD group due to missing age data.

Strata with the same superscript are statistically significantly different from one another at the indicated level:

P-value:

a, b, e, f, g: >0.05.

h, o: ≤0.05.

c, i, j, n, p: ≤0.01.

d, k, l, m: ≤0.005.

e.g., for females aged ≤60 years and diagnosed via a PR pathology laboratory, the relative frequency of oral cancer (22.7%) was not statistically different from the relative frequency for females aged ≤60 years who were diagnosed at Bellevue (subscript 'a,' i.e., p>0.05), but statistically different than females of the same age diagnosed at NYUCD (subscript 'c,' i.e., p≤0.01).