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The Journal of Registry Management is indexed in the National Library of Medicine’s MEDLINE database. Citations from the articles indexed, the indexing terms (key words), and the English abstract printed in JRM are included and searchable using PubMed.

For your convenience, the Journal of Registry Management is indexed in the 4th issue of each year and on the Web (under “Resources” at http://www.ncra-usa.org/jrm). The 4th issue indexes all articles for that particular year. The Web index is a cumulative index of all JRM articles ever published.
Dear Colleagues,

I am sure that COVID-19 is impacting everyone. Working remotely is not a new concept for most certified tumor registrars. However, those who are new to working remotely might need a few tips to assist with the transition. Several resources are available on NCRA’s Center for Cancer Registry Education website (http://www.cancerregistryeducation.org/other-education-no-ce-credit). Also, the NCRA Education Foundation has telecommuting toolkits at http://www.ncra-usa.org/Foundation/Links.

This issue of the Journal of Registry Management (JRM) contains 3 original manuscripts. First, Florence K. L. Tangka, PhD, and colleagues discuss operating costs in 4 sub-Saharan African registries. Next, Mei-Chin Hsieh, PhD, and coauthors evaluate the impact on reporting cervical lesions using LAST 2-tiered nomenclature. The last original manuscript from Jacqueline Mix, PhD, MPH, and associates compares HPV prevalence in rectal and anal squamous cell carcinoma data from 2014–2015.

In our Raising the Bar feature, Michele Webb, CTR, provides tips that will assist you in leveraging diversity to achieve results. This issue also contains the 2019 index.

The last 2 pages of the JRM contain the Call for Papers and Information for Authors. Submissions of manuscripts or articles are accepted at any time. The “How I Do It” section comes from readers who want to share their expertise and ideas on various topics.

Special Call for Articles

The Commission on Cancer (CoC) has released the 2020 Standards Optimal Resources for Cancer Care. Cancer registries are looking for guidance on implementing these new standards. We are seeking articles on this topic. Please share your expertise with your cancer registrar colleagues.

Regards,
Danette A. Clark, BS, RMA, AAS, CTR
Editor-in-Chief
JRMeditor@NCRA-USA.org
Cost of Operating Population-Based Cancer Registries: Results from 4 Sub-Saharan African Countries

Florence K.L. Tangka, PhD; Sujha Subramanian, PhD; Patrick Edwards, MSc; Anne R. Korir, MPH; Henry Wabinga, MD; Eric Chokunonga, DSS; Anne Finesse, MS; Margaret Z. Borok, FRCP (UK); Biying Liu, MSc; Mona Saraiya, MD, MPH; D. Maxwell Parkin, PhD

Abstract: Large differences exist in the coverage and quality of cancer surveillance systems across the world, with limited data currently available from low-resource settings. Information on the resources required to register cancer cases are needed in order for global, national, regional, and local stakeholders to adequately support cancer registry operations. The objective of this study is to estimate the cost of cancer registration and report the cost per cancer incident case, the cost per inhabitant in the area covered by the registry, and cost allocated to specific registry activities. The International Registry Costing Tool (IntRegCosting Tool) of the Centers for Disease Control and Prevention was used to assess the costs and resources used by 4 registries in sub-Saharan Africa (Zimbabwe, Uganda, Kenya, and Seychelles). The cost of registering a cancer case ranged from $9 to $96, with lower costs in low- and middle-income countries than in the high-income country. The cost of cancer registration at the population level is very low, ranging from 1 to 17 cents per person. The detailed cost information provided in this manuscript can help registries in in sub-Saharan Africa understand the cost of their registry operations and identify approaches to improve efficiency to meet program priorities. Furthermore, it provides additional evidence to inform funding and resource allocation decisions to advance cancer registration in the region.

Key words: African Cancer Registry Network, cancer registry, cost, economics, sub-Saharan Africa

Background

Cancer is a major public health problem in developing countries. In 2012, 57% (8 million) of the world’s new cancer cases and 65% (5.3 million) of the cancer deaths occurred in the less developed countries. Cancer accounts for a large proportion of health care spending, and patients often experience catastrophic expenditures and face significant barriers to treating cancer in limited-resource settings. Information from population-based cancer registries can be used to monitor the burden of cancer, develop cancer control strategies, evaluate successes of cancer screening and treatment programs, and design cost-effective interventions.

Unfortunately, large inequalities exist in the coverage and quality of cancer surveillance systems across the world, with limited data currently available in the limited-resource setting. For example, the percentage of the population covered by cancer registries that meet the quality standards for inclusion in global statistics (Cancer Incidence in Five Continents, or C5) is less than 10% in Asia, Central America, and South America, and approximately 2% in Africa. To address these inequalities, the International Agency for Research on Cancer (IARC), a specialized agency of World Health Organization, launched the Global Initiative for Cancer Registry Development (GICR) in 2011. The main goal of GICR is to increase global capacity for cancer registration via establishment of 6 regional resource centers or hubs to provide technical support and guidance for strengthening the ability to collect, analyze, and disseminate cancer data by population-based cancer registries. One of the 6 hubs is the African Cancer Registry Network (AFCRN), IARC, within its framework for the GICR, partners with the AFCRN to improve the quality of cancer surveillance in sub-Saharan Africa by: (1) providing technical and scientific support to countries; (2) delivering tailored training in population-based cancer registration and use of data; (3) promoting cancer registration in the region and facilitating associations and networks of cancer registries; and (4) coordinating international research projects and disseminating findings. The AFCRN currently has 30 members from 23 sub-Saharan African countries. One of the AFCRN membership eligibility criteria is achievement of at least 50% coverage of the target population, and increasing coverage to least 70% within 3 years of joining the AFCRN.

Information on the resources required to register cancer cases is needed in order for global, national, regional, and local stakeholders to adequately support cancer registry operations. Although 2 prior studies have reported on the...
cost of cancer registration in sub-Saharan Africa,\textsuperscript{13,14} there has been no systematic assessment of the value of resources required for specific registry activities across multiple sub-Saharan African countries. One of these studies assessed funding of cancer registration in sub-Saharan Africa\textsuperscript{15} and reported US $8 to $9 to register a cancer case in 2013. This study underestimated the true cost of registering a cancer case, as in-kind contributions, value of donated services, and overhead costs were not included. The other study reported the true cost of cancer registry operations from only 2 population-based cancer registries in East Africa (US $15.62 to register a cancer case in Nairobi over 2012 to 2014 and US $10.22 to register a cancer case in Kampala during 2014)\textsuperscript{14} and the extent to which the findings are generalizable to other registries in Africa is not clear.

The objective of this study is to estimate the cost of cancer registration in Africa, including the cost per cancer incident case, the cost per inhabitant in the area covered by the registry, and cost allocated to specific registry activities. Our study will provide the evidence base on the total resources required to sustain registry operations and allow for comparative assessments of registry operations across registries to identify approaches to improve efficiencies.

Methods

The International Registry Costing Tool (IntRegCosting Tool) from the Centers for Disease Control and Prevention, described previously,\textsuperscript{15} was used to assess the costs and resources used by African cancer registries. This Web-based costing tool builds on a prior Excel-based tool and was pilot tested in 10 registries in Asia, Africa, the Caribbean, and South America. Lessons learned from these prior rounds of pilot testing were incorporated in developing the Web version of the costing tool.\textsuperscript{15,16} A convenience sample of 4 population-based cancer registries from sub-Saharan African countries was selected to complete the Web-based IntRegCosting Tool. The selected AFCRN registries vary in terms of their number of years of operation, geographic location in sub-Saharan Africa, organizational structure (eg, integral part of ministry of health), income category, geographic area covered, and case volume. The 4 registries included in this study are the Nairobi Cancer Registry (in Kenya), Kampala Cancer Registry (in Uganda), the Seychelles National Cancer Registry, and the Zimbabwe National Cancer Registry (which incorporates data from population-based registries in Harare and Bulawayo, as well as data from hospitals elsewhere in the country).

The cancer registries all participated in an introductory webinar to ensure consistency between the registries in understanding the components of the costing tool. The registries received usernames and passwords to access their registry’s Web-based costing tool account. Information on costs and resources used, along with registry characteristics, was entered into 10 data modules across the Web tool. Data modules included registry background information such as funding sources, data collection approach, registry personnel, personnel activities, other personnel (such as consultants); computers, travel, training and other materials; software licensing; overhead or indirect costs; and narrative feedback. Registries received a user’s guide and ongoing technical assistance during the data collection phase. The user guide included detailed definitions that described each cancer registry activity and provided examples. Each module in the Web tool had a series of embedded data quality checks in order to ensure accurate and consistent entries. For example, we ensured that date fields contained numbers that were within specified ranges. Once all pages were validated, the tool’s built-in data analytic procedures automatically assessed the consistency across modules in terms of data entry (for instance, expenditures could not be more than the total of external funding and host contributions). The tool automatically summarized the results and produced a series of reports. Registries were able to review their summary reports to ensure the accuracy of the costing information.

Reports included the distribution of registry resources by budget category, distribution by source, distribution by registry activity, cost per case, and cost per inhabitant. Cost data were reported for 2015 for Kampala, Zimbabwe, and Seychelles, and 2013 for Nairobi. Cancer incident cases were reported for 2 years prior to the year that cost data were reported, and correspond to 2013 for Kampala, Zimbabwe, and Seychelles, and 2011 for Nairobi. This approach was performed because cases are often processed over several years, which delays the reporting of complete cases and is consistent with methods used to calculate cost-per-case information for US cancer registries.\textsuperscript{16,17} After registries reviewed and confirmed their data inputs, researchers also reviewed the data to ensure that the information was entered correctly on each screen, and to confirm that results did not drastically differ for registries that participated in prior rounds. We show the descriptive statistics and costing results of the participating African cancer registries based on data collected in the IntRegCosting Tool.

Results

Table 1 presents key characteristics of participating African registries in terms of coverage, case volume, and registry data collection methods. Table 1 shows that there is substantial variation by registry in nearly every characteristic collected, including country income category, structure, and coverage. Seychelles is the newest registry, with just 9 years of operation, compared to the registry in Kampala, which has been in operation for approximately 63 years. Seychelles and Zimbabwe national registries are based out of health departments, while Kampala is based out of a public university, and Nairobi out of the Kenya Medical Research Institute. As the Zimbabwe National Registry covers the entire country, the registry has the highest population coverage (about 13,061,239), followed by Nairobi (3,400,000), Kampala (2,700,000), and Seychelles (96,858). Zimbabwe also covers the largest area (about 390,757 km$^2$) compared to Seychelles, which has the smallest geographic coverage (459 km$^2$).

Zimbabwe had the highest number of incident cancer cases, with 6,548 cases in 2013, followed by Nairobi (2,099), Kampala (1,735), and Seychelles (172). Kenya is the only country out of the 4 where cancer is a notifiable disease.
by legislation; however, this is not actively enforced. All 4 registries meet the quality thresholds necessary for inclusion in CI5. Seychelles has 10 data sources, and since the district health centers are used as referral centers, most cases are sent to the main hospital for confirmation of diagnosis. These sources include the island’s hospitals, health information/statistic unit private clinics, hospice, laboratory, death certificate source, along with an oncology unit. Nairobi has 24 total sources that report cancer cases to the registry, followed by Zimbabwe with 23 sources and Kampala with 11 sources. All registries except Nairobi perform some level of follow-up to identify status of cancer patients after treatment. All registries except Kampala perform death clearance. Overall, the Zimbabwe registry has the most sources of funding (n = 5), while the remaining registries each have 2 sources.

The distribution of registries’ resources by budget category is presented in Figure 1. There are significant

<table>
<thead>
<tr>
<th>Country</th>
<th>Kampala Cancer Registry</th>
<th>Zimbabwe National Registry</th>
<th>Nairobi Cancer Registry</th>
<th>Seychelles National Cancer Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income category</td>
<td>Uganda</td>
<td>Zimbabwe</td>
<td>Kenya</td>
<td>Seychelles</td>
</tr>
<tr>
<td>Years of operation</td>
<td>63</td>
<td>32</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Host institution type</td>
<td>Public university</td>
<td>Health department</td>
<td>Research institute (government)</td>
<td>Health department</td>
</tr>
<tr>
<td>Population covered</td>
<td>2,700,000</td>
<td>13,061,239</td>
<td>3,400,000</td>
<td>96,858</td>
</tr>
<tr>
<td>Area covered (km²)</td>
<td>1,914</td>
<td>390,757</td>
<td>695</td>
<td>459</td>
</tr>
<tr>
<td>Cancer cases</td>
<td>1,735</td>
<td>6,548</td>
<td>2,099</td>
<td>172</td>
</tr>
<tr>
<td>Reportable disease</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If yes, actively enforced?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer Incidence in Five Continents (CI5) inclusion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of sources (total)</td>
<td>11</td>
<td>23</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Perform active follow-up</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Performs death clearance</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sources of funding</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Cancer cases corresponds to the number of cancer incidence cases and were provided by registries for the following years: Kampala, 2013; Zimbabwe, 2013; Nairobi, 2011; Seychelles, 2013. Other characteristics were provided for the following years: Kampala, 2015; Zimbabwe, 2015; Nairobi, 2013; Seychelles, 2015. Income category determined based on 2017 World Bank classification system available at https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Years of operation are the total operating years as of 2017.

Figure 1. African Registries’ Resources by Budget Category

Costs were reported by cancer registry representatives for the following annual periods: Kampala, 2015; Zimbabwe, 2015; Nairobi, 2013; Seychelles, 2015. Other personnel relates to the activities performed by consultants or through contract to external personnel not from within registry.
differences in the distribution of each registry’s resources. Both Nairobi and Zimbabwe allocate the majority of their resources towards the registry personnel budget category (60% and 55%, respectively), while Kampala and Seychelles both allocate much smaller portions towards personnel than their other budget categories (22% and 37%, respectively). Kampala’s largest budget category is toward indirect resources (overhead costs), which takes 36% of all resources and includes specific components such as rent and utilities. Seychelles’ largest budget category is for computers, travel, training, and other materials, which take 40% of all registry resources.

Figure 2 shows the distribution of registry resources by core activities, those which are the primary duties performed by the registry. Out of Kampala’s core registry activities, 61% of registry resources went toward data collection and abstraction; 16% toward data entry, validation, and consolidation; 16% toward database management and reporting; and 7% toward quality control. Zimbabwe National Registry had a higher proportion of registry core activities’ resources allocated to data collection and abstraction (68%); followed by data entry, validation, and consolidation (28%); database management and reporting (3%); and quality control (1%). In contrast, Nairobi Cancer Registry had 25% of registry resources go toward data collection and abstraction. Nairobi’s highest cost core activity was data entry, validation, and consolidation, in which 49% of resources were allocated. About 16% of Nairobi’s core resources went toward database management and reporting, and 10% went toward quality control. Seychelles National Cancer Registry had a majority of its resources for core registry activities go towards data collection and abstraction (34%), followed by data entry, validation, and consolidation (29%); database management and reporting (23%); quality control (8%); and death certificate clearance (7%).

Registries’ cost per case by budget category, total cost per case, and total cost per inhabitant are shown in Table 2. The Seychelles National Cancer Registry, the lone registry studied from a high-income country, has the highest cost per case and inhabitant. The registry costs about $96 per cancer case and about $0.17 per inhabitant in the registry coverage area. The Nairobi Cancer Registry, from a lower-middle income country, has a cost per case of about $33 and a cost per inhabitant of $0.02. The Zimbabwe National Registry, from a low-income country, had a cost per case of a little over $10, and a cost per inhabitant of less than $0.01. The Kampala Cancer Registry had the lowest cost per cancer case, about $9, and a cost per inhabitant of $0.01.

Discussion

Our study provides evidence that there is variation in the cost of operating population-based cancer registries in sub-Saharan Africa. The cost of processing a cancer case and cost per person in the geographic area the registry serves was lower in low- and middle-income countries (Uganda, Zimbabwe and Kenya) compared to the high-income country (Seychelles). Recent studies of economic evaluation of cancer registries report similar findings. In the analysis of factors affecting cost of operating cancer registries in the United States, case volume, quality of cancer incidence data, and size of area served were main drivers of cost per case registered. An earlier study summarized findings from qualitative interviews on additional factors that could influence the cost of registry operations. These factors include funding cycle (continuous in-country funding vs intermittent external funding), and organizational structure (cancer registries embedded in larger institution such as hospital or university), volume of cases, number of reporting sources, size of area served and presence of rural areas, cost of living, number and type of data elements collected, staff turnover and training requirements, method of case finding (active
vs passive), method of data abstractions (generally using paper forms rather than electronic devices), work mix (core data collection versus research activities), quality of data from reporting facilities, data exchange, reporting of nonresidence cases, annual renewal of agreements for data collection, and cancer incidence reporting mandated by law.

Some of these factors are internal to registry operations and can therefore be modified by registry management. For instance, measures can be taken toward attracting and retaining qualified staff. This may, in the long run, increase registry operational efficiencies and reduce cost. Other features external to registry operations, such as size of area served and distance to data sources, are beyond the control of registry management and could explain variation in cost. One factor that may account for the lower cost per case in Zimbabwe is that data collection is through passive notification from hospitals nationwide, with the exceptions of Harare and Bulawayo, which both perform active data collection. This allows the registry to collect a larger volume of cancer cases throughout the entire country, potentially achieving some economies of scale.

Another major finding is that, for cost of cancer registration at the population level, variation across the registries is very low, with a maximum cost of less than one-fifth of US $1 per person in the geographic area the registry serves. This is similar to findings from a recently completed analysis of cost of cancer registration in low-, lower-middle-, and upper-middle-income countries. Seventeen cents (US $0.17) is a small investment per capita compared to the gains from use of cancer registry data to inform comprehensive cancer control efforts—prevention, early detection and treatment—that could lead to reduction in health and financial burden from cancer.

Though this study provides information on the true cost of cancer registry operation in sub-Saharan Africa, it has some limitations. First, our sample is small, consisting of only 4 registries in sub-Saharan Africa (members of the AFCRN). Although the registries were selected to be representative, the sample is not large enough to capture all potential differences among sub-Saharan African registries. Thus, the findings from this study may not be generalizable to all registries in the region or registries that belong to the AFCRN. A second limitation of the data analysis presented in this study is that the registries reported their cost data and activities performed retrospectively. Retrospective cost data collection may lead to potential recall bias, as exact costs depended on registries’ quality of record keeping and the activity-based costs depended on staff’s ability to accurately estimate the portion of their time they spent on various registry activities over a period of time. Inaccuracies in the cost data were minimized through registries’ use of accounting records to extract specific costs incurred. A third limitation is the diversity of the registries. Although the costs were converted from local currencies to US dollars to allow for comparison across registries, differences in cost across registries may still remain. A fourth limitation is that registry activities—provided in this manuscript can help

<table>
<thead>
<tr>
<th>Registry</th>
<th>Low Income</th>
<th>Lower-Middle Income</th>
<th>High Income</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kampala Cancer Registry</td>
<td>1.90</td>
<td>5.70</td>
<td>35.68</td>
</tr>
<tr>
<td>Zimbabwe National Registry</td>
<td>2.29</td>
<td>0.72</td>
<td>3.16</td>
</tr>
<tr>
<td>Nairobi Cancer Registry</td>
<td>1.80</td>
<td>9.63</td>
<td>38.26</td>
</tr>
<tr>
<td>Seychelles National Cancer Registry</td>
<td>0.01</td>
<td>2.59</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Costs were reported by cancer registry representatives for the following annual periods: Kampala, 2015; Zimbabwe, 2015; Nairobi, 2013; Seychelles, 2015. Cancer cases correspond to the number of cancer incidence cases during the following years: Kampala, 2013; Zimbabwe, 2013; Nairobi, 2011; Seychelles, 2013.
registries in sub-Saharan Africa understand the cost of their operations and identify approaches to improve efficiency to meet program priorities. This information will be especially useful as Nairobi is expanding into a national registry, and Uganda is working to establish 2 new population-based registries. The new and expanded registries can leverage the experiences and lessons learned from previous cancer registration operations to develop synergies and to maintain an efficient collection of cancer cases in the growing regions. Additionally, the cost results provide additional evidence to inform funding and resource allocation decisions to advance cancer registration in the region.

References
Abstract: Background: Since 2012, the Lower Anogenital Squamous Terminology (LAST) Project recommended a 2-tiered nomenclature, low-grade and high-grade squamous intraepithelial lesion (LSIL and HSIL), to replace the 3-tiered cervical intraepithelial neoplasia (CIN) system for HPV-associated lesions. Prior to 2019, preinvasive cervical lesions classified as CIN3, severe dysplasia, carcinoma in situ (CIS), and adenocarcinoma in situ (AIS) were considered reportable to the Louisiana Tumor Registry for a CIN3 project funded by the Centers for Disease Control and Prevention (CDC); but lesions classified exclusively as high-grade/HSIL based on the 2-tiered system were not considered reportable. Due to the terminology changes, we wanted to know whether pre-2019 reportable criteria need to be modified to capture all reportable precancerous cervical cases diagnosed in 2019 forward. Objectives: To evaluate the utilization of LAST 2-tiered classification, low-grade and high-grade squamous intraepithelial lesion, and p16 immunohistochemistry (IHC) testing on cervical biopsy/surgical specimens, assess the search criteria needed to identify high-grade lesions for the CDC-funded CIN3 project, and assess the impact of underreporting cervical lesions caused by terminology changes. Methods: An equal number of abnormal/precancerous and normal cervical findings from biopsy pathology reports received in 2015 were randomly selected by an artificial intelligence (AI) search engine developed by Artificial Intelligence in Medicine Inc (AIM) using pre-2019 search criteria. Selected pathology reports were reflagged for the reportability by AIM audit software based on 2019 search criteria and manually reviewed for the use of reportable terms including CIN3, severe dysplasia, CIS, AIS, high-grade/HSIL terminology, and CIN2 or CIN2-3 with positive p16 IHC testing. Cohen’s kappa statistic was used to assess the agreement between AIM auto-coding and manual review. Positive predictive values (PPV) and sensitivity tests were computed to evaluate the reportable terms. Results: Six out of 9 surveyed laboratories used 2-tiered terminology on cervical biopsy pathology reports and 7 performed p16 IHC tests. Of 1,974 randomly selected reports from 5 laboratories, 987 were flagged as precancer by AI using pre-2019 search criteria. After adding the high-grade/HSIL term into pre-2019 search criteria, precancerous reports increased by 29%. After manual review, 41.6% of these cases were reportable precancerous cervical cases with a PPV of 0.65 (95% CI, 0.62–0.67) and 13.6% had p16 IHC performed. Conclusions: Both the 2-tiered and 3-tiered nomenclature are needed to ensure complete identification of all reportable high-grade cervical lesions.

Key words: cervical intraepithelial neoplasia, cervical precancer, high-grade, p16 IHC staining, squamous intraepithelial lesions

Introduction

The main risk factor for acquiring precancerous cervical lesions is human papillomavirus (HPV) infection and over 95% of cervical neoplasia are HPV-related worldwide.1-4 In 2006, the US Food and Drug Administration licensed the HPV vaccine for use in females aged 9 to 26 years.5 Findings from the HPV-IMPACT study showed significantly decreased incidence rates of high-grade cervical intraepithelial neoplasia (CIN2-CIN3) and carcinoma in situ (CIS) among women aged 18 to 29 years after HPV vaccine introduction.6 Due to increased understanding of HPV molecular biology and cervical carcinogenesis association, and apparent subjectivity when differentiating CIN2 and CIN3, the Lower Anogenital Squamous Terminology (LAST) Standardization Project, which was cosponsored by the College of American Pathologists and American Society for Colposcopy and Cervical Pathology, recommended the 2-tiered classification system, low-grade squamous
intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), for reporting histopathology from biopsies of all lower anogenital tract HPV-related squamous lesions in 2012. This 2-tiered system was also endorsed by the World Health Organization (WHO) because it was more biologically relevant and more histologically reproducible than the 3-tiered CIN1 (mild dysplasia), CIN2 (moderate dysplasia), and CIN3 (severe dysplasia) system.

The LSILs are usually HPV infections that are self-limited, while the HSILs may progress to invasive carcinoma. Additionally, the LAST Standardization Project proposed use of p16 immunohistochemistry (IHC) staining to classify equivocal lesions into either LSIL if negative staining or HSIL if positive.7

Before 1996, CIN3, CIS, and adenocarcinoma in situ (AIS) of the cervix were reportable to central cancer registries in the United States; however, these cervical lesions were no longer required to be collected and reported to the nation in 1996. In order to assess the association of HPV vaccination with precancerous cervical lesions in statewide populations, the Centers for Disease Control and Prevention (CDC) funded 4 central cancer registries, including the Louisiana Tumor Registry (LTR), to collect preinvasive cases diagnosed in 2009 and onward.9 The eligible precancerous cervical lesions diagnosed before 2019 for this CDC-funded CIN3 project included CIN3, severe dysplasia, CIS, and AIS, and over 93% of cases were diagnosed either as CIN3 or severe dysplasia in Louisiana. Pathology reports containing the high grade or HSIL terminology were not initially considered reportable unless CIN3/severe dysplasia/CIS terminology was also documented. If pathologists solely used the 2-tiered LSIL/HSIL classification for cervical precancers since 2012, then the pre-2019 eligibility criteria, which is currently being used to define reportable cervical precancers for the CIN3 project, would not have captured all eligible cases diagnosed in 2012 and after.

To help address these issues, the LTR conducted an audit on cervical pathology reports in 2018 to evaluate use of the 2-tiered classification and p16 IHC test. The study objectives were to: (1) survey pathology laboratory results to determine use of the 2-tiered nomenclature when classifying precancerous cervical lesions; (2) evaluate information in pathology reports on recommended p16 IHC testing; (3) assess the additional search criteria needed when screening pathology reports to identify eligible cervical precancers diagnosed in 2019 and after; and (4) measure the impact of underreporting caused by terminology changes on reportable cervical precancers.

Materials and Methods

Data Source

Electronic pathology (e-path) reports received in 2015 for patients residing in Louisiana were used to conduct this audit. Only pathology reports from cervical biopsy specimens or specimens obtained from surgical procedures—including electrocautery, ablative and excisional procedures, endocervical curettage, loop electrocautery excision procedure, and hysterectomy—were included. This CDC-funded project was interested in the histopathologically confirmed CIN3 cases only; therefore, cytology reports were excluded. Louisiana state law authorizes LTR to collect all cancer-related data from medical records, including pathology reports, and conduct research. We received institutional review board (IRB) approval from the Louisiana State University Health Sciences Center—New Orleans to use LTR data for this study.

Surveying Pathology Laboratories

Ten pathology laboratories, including 2 national laboratories with a high volume of precancerous cervical cases in Louisiana, were invited to participate in this study. These laboratories use either Artificial Intelligence in Medicine, Inc (AIM) developed E-path Reporter or the CDC-provided Public Health Information Network Messaging System (PHIN-MS) for their e-path reporting. Three questions, along with subquestions related to the use of 2-tiered terminology and molecular testing, were developed (Table 1). The survey was conducted via phone interviews.

Defining Search Criteria and Eligible Cases

The search criteria are used to identify potential cervical precancers from pathology reports. All possible diagnosis terms related to precancerous cervical lesions were included in the search criteria. Prior to 2019, the search criteria (pre-2019 search criteria) included International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes C53.0–C53.9, microscopically confirmed with the following terms: CIN3, CIS, AIS, grade 3, any in situ epithelial tumors, and/or severe dysplasia documented in combination with p16 IHC staining for CIN2 cases.

<table>
<thead>
<tr>
<th>Survey Questions</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are pathologists using the recommended LAST 2-tiered terminology (HSIL/LSIL) on biopsy reports?</td>
<td>Yes No</td>
</tr>
<tr>
<td>1a. Do pathologists also document the CIN2 or CIN3 classification in addition to the LAST terminology in the pathology reports?</td>
<td>6 3</td>
</tr>
<tr>
<td>2. Are pathologists performing p16 IHC staining for CIN2 cases?</td>
<td>7 2</td>
</tr>
<tr>
<td>2a. If so, is this done in house?</td>
<td>7 0</td>
</tr>
<tr>
<td>2b. Is p16 available on pathology report?</td>
<td>7 0</td>
</tr>
<tr>
<td>3. Are pathologists performing Ki-67 (grading), ProEx C or other IHC staining either alone or in combination with p16 IHC staining for CIN2 cases?</td>
<td>5 4</td>
</tr>
<tr>
<td>3a. If so, what type?</td>
<td>Ki-67 NA</td>
</tr>
<tr>
<td>3b. Is Ki-67 or ProEx C or other IHC available on pathology report?</td>
<td>5 0</td>
</tr>
</tbody>
</table>

CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry; LSIL, low-grade squamous intraepithelial lesion.
from cervical biopsy/surgical specimens. The new search criteria for 2019 include pre-2019 search criteria plus the following new terminologies: high-grade, high-grade squamous intraepithelial lesions (HSIL or HGSIL), CIN2, CIN2-3, CIN2/3, and/or p16 IHC test with cervix.

The eligible cases (or reportable cases) for pre-2019 are CIN3, severe dysplasia, CIS, and AIS. For 2019, the eligible cases include pre-2019 eligible cases plus precancers diagnosed based on the following reportable terms: HSIL, high-grade, and CIN2 or CIN2-3 with positive p16 IHC staining. Eligibility/search criteria and reportable terms for precancerous cervical lesions diagnosed before 2019 and in 2019 are summarized in Figure 1.

**System Used to Perform Audit**

We used a standalone pathology report audit software developed by AIM to perform this audit. This system uses natural language processing (NLP) to interpret the content of pathology reports based on the provided terminologies (search criteria) and the artificial intelligence (AI) engines perform content coding and report selection. Search criteria were programmed into AIM audit system to flag potentially eligible cervical precancers from pathology reports for manual review. Eligible cases and reportable terms identified through manual review were entered into the AIM audit software.

**Manual Review Processing**

Pathology reports with either a precancerous or normal finding identified by AIM software were reviewed by a clinician and/or a certified tumor registrar who had extensive experience reading pathology reports. These manual reviews were conducted in order to determine which pathology reports met pre-2019 and 2019 reportable terms for eligible cases. The reportable precancerous terms were recorded for each eligible case and then were categorized into 3 terminology subgroups: pre-2019 reportable terms.
only (CIN3, CIS, severe dysplasia, and AIS), new reportable terms only (HSIL, high-grade, and CIN2 or CIN2-3 with positive p16 IHC staining), and the combination (2019 reportable terms). The presence of p16 IHC testing and the subsequent results of p16 IHC staining were collected and coded. CIN2 and CIN2/3 without high-grade term, without p16 IHC test performed, or with negative p16 test were not considered reportable as precancer for this project. Cervical precancerous lesions identified solely based on Papanicolaou (Pap) test reports, with previous invasive cervical cancer, or followed by an invasive cervical cancer within 12 months were not reportable and excluded.

**p16 Immunohistochemistry Staining and Test Results**

We developed 5 different codes to classify p16 IHC staining status and result: *test not performed, negative, positive, indeterminate, and unknown test result*. The indeterminate category was used when we were unable to determine whether the p16 IHC test was positive or negative based on terms in the pathology report. The positive test result was used when the pathology report described p16 staining as block-positive (strong and diffuse block staining), full-thickness staining of the squamous epithelium or strong nuclear and cytoplasmic staining of the basal mucosa with extension to at least one-third of epithelial thickness. The negative test result was applied to cases in which p16 staining was reported as weak, focal, patchy, cytoplasmic only, or staining confined to only basal layer.

**Statistical Analysis**

The frequency distributions including the proportions of reportable terminologies were generated for reportable cervical precancers by pathology laboratory. We also calculated the percentages of pathology reports with the p16 IHC test performed by the laboratory. We used Cohen’s kappa statistic to assess the agreement between AIM and manual
review. The positive predictive value (PPV) and negative predictive value (NPV) as well as sensitivity and specificity based on AIM’s selection versus manual review (as the reference standard) were computed to assess the predictability and degree of discrepancy for reportability. Finally, the \( \chi^2 \) test was used to assess the association between p16 IHC testing and terminology group. Data analysis was carried out using SAS v 9.4 (SAS Institute, Inc).

**Results**

Nine out of 10 laboratories participated in our survey. Six laboratories used the 2-tiered terminology on cervical biopsy pathology reports and the remaining laboratories used it for cytology reports (Pap test) only (Table 1). Of the 6 laboratories that used the 2-tiered terminology, 5 of them used it in combination with CIN terminology. Seven laboratories performed p16 IHC tests and 5 of them also performed Ki-67 tests. All laboratories that reported using p16 IHC and Ki-67 testing included test results in their pathology reports even if this testing was not done in house.

Five pathology laboratories, which cover 51% of Louisiana’s annual case count for reportable precancerous cervical lesions and use both 2-tiered and CIN 3-tiered terms, were included in the audit. A total of 1,974 pathology reports (987 abnormal/precancerous and 987 normal reports) were randomly selected by AIM audit software based on pre-2019 search criteria from these laboratories. After implementing 2019 search criteria into AIM audit software, 1,273 previously selected pathology reports were flagged as precancer cases, which increased the number of potential reportable cases for manual review by 29%. After manual review, 822 (41.6%) reports met 2019 reportable criteria (combination of pre-2019 and new reportable terms).

The percentage of agreement was 77.2% with a kappa statistic of 0.56 (95% CI, 0.53–0.60), moderate agreement, and a PPV of 0.65 (95% CI, 0.62–0.67). The estimated NPV was 1.00 (95% CI, 0.995–1.000), which indicated all normal reports flagged by AIM were nonreportable. The sensitivity for correctly identifying reportable cases was 1.0 (95% CI, 0.996–1.000); however, the specificity was low at 0.61 (95% CI, 0.58–0.64).

Of 822 eligible cases identified through manual review, 129 (15.7%) contained pre-2019 reportable terms only, 347 (42.2%) were solely based on the new reportable terms, and 346 (42.1%) included both pre-2019 and new reportable terms (Figure 3). Including new reportable terms for precancerous cervical lesions resulted in a 73% increase in reportable cases. Pathology laboratories varied in their use of reportable terminologies, ranging from 3.9%–49.1% based on the pre-2019 terms only, 19.3%–47.3% based on new reportable terms only, and 27.7%–54.9% based on 2019 reportable terms (both pre-2019 and new terms) in pathology reports.

Table 2 presents the frequency distribution of usage of reportable terminology by pathology laboratory. In general, the most frequently used terms were HSIL (or HGSIL) (59.3%) followed by CIN3 (49.5%) and high-grade (46.7%). Laboratory #5 used the “HSIL” term in the majority (93.1%) of their reportable pathology reports and laboratory #2 favored using “high-grade” (Table 2). About 6.5% of reportable cases had CIN2-3 with a positive p16 test and 5.8% had CIN2 with a positive p16 result in pathology reports. We further examined those 347 reportable cases identified from new reportable terms only; all of them except 1 (identified through positive p16 IHC for CIN2-3) had either HSIL or high-grade terminology documented in the pathology report.

**Figure 3. Use of Reportable Terms Identified in 2015 Pathology Reports by Selected Pathology Laboratories in Louisiana**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Lab 1 (N=201)</th>
<th>Lab 2 (N=184)</th>
<th>Lab 3 (N=57)</th>
<th>Lab 4 (N=176)</th>
<th>Lab 5 (N=204)</th>
<th>Total (N=822)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>15.4</td>
<td>29.4</td>
<td>49.1</td>
<td>5.3</td>
<td>3.9</td>
<td>15.8</td>
</tr>
<tr>
<td>10-20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>60-70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-80</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>80-90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>37.3</td>
<td>27.7</td>
<td>31.6</td>
<td>50.6</td>
<td>54.9</td>
<td>42.0</td>
</tr>
</tbody>
</table>

* Pre-2019 reportable terms * New reportable terms 2019 reportable terms *

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN2-3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry.
and 19.6% only included the HSIL/high-grade terminology without the CIN terminology (Figure 4). Additionally, of 346 reportable cases containing a combination of terms, 90.1% were CIN3 with HSIL/high-grade combination.

Among audited pathology reports, 268 (13.6%) had p16 IHC staining performed and 71.3% of these had positive staining (Table 3). Use of p16 IHC staining by laboratory ranged from 0% to 26.6% (Table 3) and it was also significantly associated with type of terminology group ($P < .0001$) (Figure 5). Precancerous cervical lesions identified solely through the new reportable terminology had a higher percentage of p16 tests performed (36.9%) than those identified through pre-2019 terminology (6.9%) or using a combination of term (15.9%).

**Table 2. Frequency Distribution of Reportable Terminology by Pathology Laboratory**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Lab 1 (n = 201)</th>
<th>Lab 2 (n = 184)</th>
<th>Lab 3 (n = 57)</th>
<th>Lab 4 (n = 176)</th>
<th>Lab 5 (n = 204)</th>
<th>Total (n = 822)</th>
<th>Contained Pre-2019 Terms (n = 475)</th>
<th>Based on New Terms Only (n = 347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contained Pre-2019 terms</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
</tr>
<tr>
<td>1. AIS</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (3.5)</td>
<td>0 (0.0)</td>
<td>11 (5.4)</td>
<td>15 (1.8)</td>
<td>15 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td>2. CIN3</td>
<td>81 (40.3)</td>
<td>93 (50.5)</td>
<td>43 (75.4)</td>
<td>83 (47.2)</td>
<td>107 (54.5)</td>
<td>407 (49.5)</td>
<td>407 (85.7)</td>
<td>0</td>
</tr>
<tr>
<td>3. CIS</td>
<td>9 (4.5)</td>
<td>11 (6.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (2.0)</td>
<td>24 (2.9)</td>
<td>24 (5.1)</td>
<td>0</td>
</tr>
<tr>
<td>4. Severe dysplasia</td>
<td>18 (9.0)</td>
<td>1 (0.5)</td>
<td>1 (1.8)</td>
<td>15 (8.5)</td>
<td>2 (1.0)</td>
<td>37 (4.5)</td>
<td>37 (7.8)</td>
<td>0</td>
</tr>
<tr>
<td>5. HSIL</td>
<td>107 (53.2)</td>
<td>53 (28.8)</td>
<td>25 (43.9)</td>
<td>112 (63.6)</td>
<td>190 (93.1)</td>
<td>487 (59.3)</td>
<td>278 (58.5)</td>
<td>209 (60.2)</td>
</tr>
<tr>
<td>6. High grade</td>
<td>104 (51.7)</td>
<td>101 (54.9)</td>
<td>13 (22.8)</td>
<td>126 (71.6)</td>
<td>40 (19.6)</td>
<td>384 (46.7)</td>
<td>170 (35.8)</td>
<td>214 (61.7)</td>
</tr>
<tr>
<td>7. CIN2-3 with p16+</td>
<td>29 (14.4)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>21 (11.9)</td>
<td>2 (1.0)</td>
<td>53 (6.5)</td>
<td>5 (1.1)</td>
<td>51 (14.7)</td>
</tr>
<tr>
<td>8. CIN2 with p16+</td>
<td>14 (7.0)</td>
<td>20 (10.9)</td>
<td>0 (0.0)</td>
<td>8 (4.6)</td>
<td>6 (2.9)</td>
<td>48 (5.8)</td>
<td>7 (1.5)</td>
<td>41 (11.8)</td>
</tr>
</tbody>
</table>

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; CIN2-3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; lab, laboratory.

### Discussion

Population-based cancer registries use the cervical biopsy pathology report as the main data source for timely collecting reportable cervical precancers. Due to the change in pathologists’ practices for documenting HPV-associated precancerous cervical lesions and the increasing use of the 2-tiered terminology, reporting of cervical precancers using only the CIN designation led to underreporting of high-grade lesions by population-based cancer registries since 2012. The new eligibility criteria (2019 criteria) for precancerous cervical lesions, implemented through the AIM audit software, had a sensitivity of 100%, which most likely did not omit any reportable pathology reports. Yet, by using the new eligibility criteria, there was a tradeoff of low specificity (61%) which 39% of nonreportable cases were flagged as reportable for manual review.

While all 5 selected laboratories reported using both CIN 3-tiered and LAST and WHO recommended 2-tiered terminology systems in their cervical histopathology reports, some pathologists could use either 2-tiered or CIN terminology alone to classify cervical lesions in biopsy pathology reports. Our audit found the use of 2-tiered system varied by laboratories. Overall, 84.1% of reportable pathology reports received in 2015 contained the high-grade or HSIL terms with range from 50.9% to 96.1%. Although we did not collect information on 2-tiered system usage by pathologists, the findings from a single large academic pathology practice showed the variation of increasing use of HSIL in cervical biopsy specimens before and after the implementation of 2-tiered terminology among pathologists. The range of differences in increasing 2-tiered system use were from 0.1% to 9.6%.10

It is well recognized that the diagnosis of cervical pathology using the CIN 3-tiered classification is subjective and varies by pathologist, especially in CIN2 cases.11-14 Several studies have shown the low interobserver reproducibility of
Table 3. Frequency Distribution of p16 Immunohistochemistry (IHC) Staining Performed Status and Test Result by Pathology Laboratory

<table>
<thead>
<tr>
<th>p16 IHC staining</th>
<th>Lab 1 (n = 500)</th>
<th>Lab 2 (n = 464)</th>
<th>Lab 3 (n = 134)</th>
<th>Lab 4 (n = 376)</th>
<th>Lab 5 (n = 500)</th>
<th>Total (n = 1974)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>Count (%)</td>
</tr>
<tr>
<td>Performed</td>
<td>93 (18.6)</td>
<td>49 (10.6)</td>
<td>0</td>
<td>100 (26.6)</td>
<td>26 (5.2)</td>
<td>268 (13.6)</td>
</tr>
<tr>
<td>Negative</td>
<td>27 (29.0)</td>
<td>17 (34.7)</td>
<td>0</td>
<td>17 (17.0)</td>
<td>5 (19.2)</td>
<td>66 (24.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>58 (62.4)</td>
<td>31 (63.3)</td>
<td>0</td>
<td>81 (81.0)</td>
<td>21 (80.8)</td>
<td>191 (71.3)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>6 (6.5)</td>
<td>0</td>
<td>0</td>
<td>2 (2.0)</td>
<td>0</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2.2)</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Not performed</td>
<td>407 (81.4)</td>
<td>415 (89.5)</td>
<td>134 (100.0)</td>
<td>276 (73.4)</td>
<td>474 (94.8)</td>
<td>1,706 (86.4)</td>
</tr>
</tbody>
</table>

IHC, immunohistochemistry; lab, laboratory.

Figure 5. Proportion of p16 IHC Testing Status by Type of Terminology Group

* Contained both pre-2019 (CIN3, severe dysplasia, CIS, and AIS) and new reportable terms (high-grade, HSIL, and CIN2 or CIN2-3 with positive p16 IHC test).

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN2-3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry.

the CIN2 distinction in both cervical cytologic and histologic interpretations, and using histopathologic criteria alone without a molecular biomarker to differentiate CIN2, may not be reliable. The use of p16 IHC tests on cervical biopsy specimens has been demonstrated to improve the accuracy of CIN diagnosis and to assist in differentiating precancer from a mimic of precancer. If the LAST recommendations were followed, estimated overall use of p16 IHC staining would be about 20% to 25% of all cervical biopsies. In our audit, 2 out of 5 audited laboratories used p16 IHC test, close to the percentage estimated by the LAST Project (18.6% and 26.6%). The average was 13.6%, which was comparable with a previous study that found 13.9%. Additionally, compared with reportable cervical precancer reports containing the CIN3 terms (pre-2019 reportable terms) only, those using high-grade terms were most likely to order a p16 IHC test (6.9% vs. 36.9%). This result implies that pathology laboratories using the 2-tiered system are also following the LAST’s recommendation to use a p16 IHC test to clarify any category considered intermediate for a cervical biopsy specimen.

By adding new reportable terms (HSIL/high-grade and CIN2 or CIN2-3 with positive p16 IHC test), eligible precancerous cervical cases diagnosed in 2015 increased 73% when compared with using pre-2019 reportable terms. In order to align with the current practice and be able to compare data collected before 2019 and after, the 2019 reportable terms include pre-2019 and new reportable terms. For the HSIL/high grade category, additional CIN terminologies will be collected. When only the HSIL/high grade terminology was documented without CIN terminology or other pre-2019 reportable terms, this will be noted in the data collection as well.

A major limitation of collecting data on high-grade cervical precancers is that changing pathological terminology can make it difficult to estimate a reliable incidence rate for precancerous cervical lesions. In general, the estimated incidence rate of HPV-related cervical intraepithelial neoplasia
has been commonly presented as low-grade neoplasia (CIN1) and high-grade neoplasia (CIN2, CIN3).\textsuperscript{21,22} A report that was able to estimate incidence rates for each CIN category used data collected from the New Mexico HPV Pap Registry, the only United States registry that captures individual CIN categories from 2007 to 2014.\textsuperscript{22} When precancerous cases determined solely based on “high-grade” terminology, this prevents researchers from studying that specific CIN category. However, this issue can be resolved if pathologists add CIN nomenclature with the basic 2-tiered classification for histopathology reports that would help to distinguish CIN2 and CIN3 from HSIL. Another limitation is that the interpretation of p16 IHC staining results in the pathology report is based on a pathologist’s experience and can be subjective.

In conclusion, findings from this audit helped to define the new eligibility criteria for reportable precancerous cervical cases for the CDC-funded CIN3 project, as well as highlighted the 2-tiered and 3-tiered nomenclature needed to ensure complete identification of all cervical precancer cases. Population-based cancer registries collecting cervical precancers should modify their reporting criteria to incorporate expert recommendations and terminology used in current practice and reporting by pathologists to ensure complete cervical precancer ascertainment in their catchment area. Most importantly, federal cancer organizations need to partner with the College of American Pathologists to provide pathologists the training and educational opportunities regarding the terminology changes and uses when reporting cervical precancers to avoid underreporting.

Acknowledgements

The authors would like to thank the hospital and freestanding pathology laboratories in Louisiana and 2 national pathology laboratories for their participation, as well as the hospital, regional and state central registrars for their diligence in cancer data collection.

References


Jacqueline Mix, PhD, MPH; Mona Saraiya, MD, MPH; Charles E. Lynch, MD, PhD; Trevor D. Thompson, BS; April Greek, PhD; Thomas C. Tucker, PhD; Edward S. Peters, ScD, DMD; Troy D. Querec, PhD; Elizabeth R. Unger, MD, PhD

Abstract: Background and Aims: Rectal squamous cell carcinoma (SCC) is a rare malignancy, and the causal role of human papillomavirus (HPV) in these cancers is thought to be similar to anal cancer. We compared type-specific prevalence of HPV in rectal SCC to anal cancer. In rectal SCC, we evaluated the agreement between HPV prevalence and positivity for p16, a marker of oncogenic activity. Methods: A stratified random sample of rectal SCCs and anal cancers diagnosed between 2014 and 2015 were identified from 3 statewide cancer registries in Iowa, Kentucky, and Louisiana. HPV testing was performed at the HPV laboratory at the Centers for Disease Control and Prevention. HPV types were described using hierarchical attribution to HPV16 and other oncogenic types, weighted for sampling design. In rectal SCC, we computed concordance and Cohen’s kappa coefficient (κ) between HPV status and p16 positivity. Results: A total of 39 rectal and 72 anal cancers were analyzed. HPV16 was the most common type in both rectal and anal cancer and did not differ significantly between sites (71.4% vs 82.1%; P = .32). Concordance between the presence of any HPV type and p16 positivity in rectal SCC was 92% with κ = 0.77. Conclusions: Rectal SCC and anal cancer have similar type-specific HPV prevalence, with HPV16 found most frequently. Substantial agreement between p16 and HPV status in rectal SCC lends additional support for the etiologic role of HPV in both anal and rectal cancer. Larger studies could be conducted to replicate these findings.

Key words: anal, cancer, HPV, human papillomavirus, rectal, squamous cell carcinoma

Introduction

Rectal squamous cell carcinoma (SCC) is a rare malignancy (comprising 1%–2% of rectal tumors) and has an incidence rate per year of 1.54 per million persons among males and 3.0 per million persons among females. Both rectal SCC and anal cancer develop near the anal transition zone where rectal and anal epithelium converge, an area particularly vulnerable to human papillomavirus (HPV) infection. Whereas 90% of anal cancers are caused by HPV, studies on HPV prevalence in rectal SCC are limited, although the association is likely to be similar. The close anatomic proximity of rectal and anal cancer makes precise distinction between rectal and anal origin difficult and misclassification of the anatomic site may occur. However, evidence suggests that rectal SCC may arise as a primary tumor. The aim of the current study was to utilize cancer tissues derived from US state cancer registries to describe the distribution of HPV types detected in rectal SCC and compare type prevalence to anal cancer. In addition, we evaluated the concordance between HPV status and over-expression of p16, a marker of HPV oncogenic activity, in rectal SCC to provide additional evidence of the role of HPV in its etiology.

Methods

Routine population-based tracking of HPV types in HPV-associated cancers is not currently conducted in the United States, but the Centers for Disease Control and Prevention (CDC) has supported 2 special HPV typing studies using statewide cancer registries. In the first study, the CDC Cancer Registry Sentinel Surveillance System (CRSSS) was developed in partnership with 7 cancer registries in Iowa, Kentucky, and Louisiana to collect HPV typing information from select cancer sites in 2014–2015. We analyzed invasive, microscopically confirmed rectal and anal cancers from the second study, which were identified by the cancer registries using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site codes: C20.9 (rectal) and C21.0–C21.8 (anal). Rectal cancers were limited to ICD-O-3 morphology codes 8050–8084 and 8120–8131. All anal ICD-O-3 morphology codes were included except for melanomas (8720–8790), sarcomas (8800–8991),...
mesotheliomas (9050–9055), Kaposi sarcomas (9140), and leukemias/lymphomas (9590–9992). Anal cancer cases were sampled by the cancer registries using a stratified random sampling design based on age (<50 years, ≥50 years) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic other). Due to their rarity, all rectal cancer cases were sampled, regardless of age or race/ethnicity. All protocols were reviewed and approved by the institutional review boards of all participating organizations and the CDC.

**Tissue Processing Histology Review and Laboratory Methods**

Tissue processing, histology review, and laboratory methods have been described previously. Briefly, central pathology laboratories associated with the cancer registries were asked to select 1 representative archived, formalin-fixed paraffin-embedded (FFPE) tissue block from each rectal and anal case. Tissue sections were prepared by taking six 5-µm sections (8 for rectal cancers) from each block and performing hematoxylin and eosin (H&E) staining on the first and last sections. All tissue blocks were processed with a standardized protocol to prevent contamination of samples.

A study pathologist reviewed submitted H&E sections to provide confirmation that intervening sections had tumor. Samples passing histologic review were extracted for DNA as previously described. All samples were tested with the Linear Array HPV Genotyping assay (LA; Roche Diagnostics) that detects 37 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52[XR], 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, IS39). Samples that were inadequate or HPV-negative were retested with the RHA kit HPV SPF-10-LiPA25, version 1 (Labo Biomedical Products B.V.) that detects 25 types (HPV 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 74). P16 immunohistochemistry (IHC) was performed using Ventana BenchMark XT automated system with monoclonal anti-p16INK4a (clone E6H4 in CINtec p16 assay, Ventana Roche) and ultraView Universal DAB Detection kit (Ventana Roche). A positive tissue control (FFPE cell pellet of HPV-positive cancer cell line) was included with each assay. Interpretation of p16 results (p16 positive, p16 negative, or inadequate) was performed by a pathologist using light microscopic examination of slides processed with and without primary antibody using criteria established by Cooperative Group Trials for Oropharyngeal Cancer. All HPV typing and p16 IHC was conducted at the CDC HPV laboratory using standardized procedures. Cancer registries provided demographic and clinical data about each case including sex, race, age at diagnosis, and SEER Summary tumor stage at diagnosis.

![Figure 1. Study Population, CDC CRSSS, 2014–2015](image-url)
Sampling weights were calculated based on the probability of selection within each registry to weight analyses to the age and race/ethnicity distributions in the underlying registry populations. Demographic characteristics were summarized using sampling weights. Age was grouped into 10-year intervals. Tumor stage at diagnosis was categorized into local, regional, distant, or unstaged using the SEER Summary Stage guidelines.7

HPV type prevalence was summarized by anatomic site. HPV types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered oncogenic.8,9 HPV types were classified using a hierarchical attribution into 3 mutually exclusive categories: (1) HPV16: positive for HPV16 regardless of single or multiple infection; (2) all other oncogenic HPV types: all cases positive for other oncogenic types except for HPV16; (3) nononcogenic or HPV negative: any other nononcogenic type that is not positive for any other oncogenic HPV type, or cases that are HPV negative. Hierarchical classification is based on a ranking of HPV types and attributes cancers to a single type group, even if multiple HPV types are detected. For this reason, we additionally examined the prevalence of single and multiple HPV infections. Ninety-five percent Wilson confidence limits around the HPV prevalence estimates were calculated. Statistical testing was performed using first order Rao-Scott χ² tests using PROC SURVEYFREQ. Statistical analysis was performed using SAS version 9.4, taking into account the stratified sampling design and allowing for weighted estimates.

We used positive p16 IHC results as supporting HPV oncogenic activity and a surrogate for HPV detection. Agreement between the detection of any HPV and p16 positivity was evaluated using concordance and Cohen’s κ coefficient. Substantial agreement has been defined as a κ coefficient from 0.61 to 0.80.10

Results
Rectal and anal cancer cases included in the study population are shown in Figure 1. During 2014–2015, a total of 66 rectal and 552 anal cancer cases were identified as eligible samples by the cancer registries. According to the proposed sample size for anal cancer, a total of 80 cases were randomly selected within age and race strata for retrieval by the cancer registries and submitted to the CDC HPV laboratory. A total of 44 rectal cancer cases were obtainable and typed. Of these, 1 rectal and 6 anal cancer cases were excluded because of ineligible histology or nonrepresentative tissue. A total of 43 rectal and 74 anal cancer cases underwent HPV testing. Typed cases were further excluded if typing was insufficient (1 rectal and 1 anal cancer case), ineligible because of an out-of-state residence (2 rectal cancer cases), or both (1 rectal cancer case). A total of 39 rectal and 73 anal cancer cases had eligible and adequate samples. For final analyses we further excluded 1 anal cancer case in order to limit the sample to white or black race/ethnicity.

Study characteristics evaluated did not differ significantly by sex, race, age, or tumor stage (Table 1). The type-specific HPV prevalence for rectal and anal cancer cases is summarized in Table 2. Any HPV type was detected in 82.4% of rectal and 90.6% of anal cancers (P = .43). Oncogenic HPV types were found in 82.4% of rectal and 88.7% of anal cancers. Nononcogenic HPV types were found in 7.3% of rectal cases and 12.5% of anal cancer cases. In 69.6% of rectal and 77.5% of anal cancer cases, a single HPV type was detected. Multiple types were detected in 12.9% in rectal and 13.2% of anal cancers. Most cases were attributed to HPV16, 71.4% and 82.1% in rectal and anal cancer, respectively. There were no statistically significant differences between rectal and anal cancer cases in any HPV type grouping examined. The overall prevalence of single HPV types detected were similar and are reported in Table 3. Concordance between detection of any HPV and p16 positivity in rectal SCC was 92%, κ = 0.77, indicating substantial agreement (data not shown).
Table 2. HPV Type Prevalence in Rectal and Anal Cancer, CDC CRSSS, 2014–2015

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>Rectal&lt;sup&gt;a&lt;/sup&gt; (n = 39)</th>
<th>Anal&lt;sup&gt;b&lt;/sup&gt; (n = 72)</th>
<th>P Value&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Any type&lt;sup&gt;e&lt;/sup&gt;</td>
<td>32</td>
<td>82.4 (67.5–91.4)</td>
<td>68</td>
</tr>
<tr>
<td>Oncogenic&lt;sup&gt;f&lt;/sup&gt;</td>
<td>32</td>
<td>82.4 (67.5–91.4)</td>
<td>65</td>
</tr>
<tr>
<td>Nononcogenic&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3</td>
<td>7.3 (2.4–19.8)</td>
<td>12</td>
</tr>
<tr>
<td>Single type</td>
<td>27</td>
<td>69.6 (53.7–81.8)</td>
<td>56</td>
</tr>
<tr>
<td>Multiple types&lt;sup&gt;h&lt;/sup&gt;</td>
<td>5</td>
<td>12.9 (5.6–26.8)</td>
<td>12</td>
</tr>
<tr>
<td>Hierarchical HPV groups&lt;sup&gt;i&lt;/sup&gt;</td>
<td>.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV16</td>
<td>28</td>
<td>71.4 (55.5–83.4)</td>
<td>53</td>
</tr>
<tr>
<td>Other oncogenic</td>
<td>4</td>
<td>11.0 (4.4–25.2)</td>
<td>12</td>
</tr>
<tr>
<td>Negative/nononcogenic&lt;sup&gt;j&lt;/sup&gt;</td>
<td>7</td>
<td>17.6 (8.6–32.5)</td>
<td>7</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; CRSSS, Cancer Registry Sentinel Surveillance System; HPV, human papillomavirus.

<sup>a</sup> Rectal cancer includes ICD-O-3 site code C20.9 and morphology codes 8050–8084 and 8120–8131.

<sup>b</sup> Anal cancer includes ICD-O-3 site codes C21.0–C21.8; morphology codes 8720–8790 (melanoma), 8800–8891 (sarcoma), 9050–9055 (mesothelioma), 9140 (Kaposi sarcoma), and 9590–9992 (leukemias / lymphomas) were excluded.

<sup>c</sup> Weighted percentages take into account sampling frame for age and race/ethnicity.

<sup>d</sup> Statistical testing performed with first order Rao-Scott $\chi^2$ statistics with $\alpha = .05$.

<sup>e</sup> Positive for any HPV type tested for.

<sup>f</sup> Positive for HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68.

<sup>g</sup> Positive for HPV types 6, 11, 26, 34, 40, 42, 43, 44, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 74, 81, 82, 83, 84, 89, or HPVIS39.

<sup>h</sup> Range of multiple types was 2–7.

<sup>i</sup> See methods section for further explanation of HPV type hierarchical classification.

<sup>j</sup> A total of 7 rectal and 4 anal cancer cases were HPV negative; 3 anal cancer cases were attributed to HPV6.

Discussion

In this study, we found HPV prevalence was high and similar for rectal (82.4%) and anal cancer (90.6%), with predominance of HPV16 (71.4% rectal, 82.1% anal). In addition, we were able to demonstrate that substantial agreement exists between presence of HPV DNA and p16 overexpression in rectal cancer, which lends support to the etiologic role of HPV in rectal SCC.

HPV has been proposed as a risk factor for rectal SCC, given its close proximity to the anal transition zone, and the known association between HPV and anal cancer. In a study of anal cancers diagnosed during 1986 to 1998 in Washington State, 13 rectal SCC were tested for HPV and 77% were found to be HPV16 positive. Another study, performing genotyping on 24 rectal SCC samples from the Hawaii and Iowa cancer registries, found that 63% tested positive for HPV16 DNA. Several small studies have also indicated the presence of HPV16; however, other case studies and small studies did not detect any HPV16. The lack of large genotyping studies investigating rectal SCC could be due to the low incidence of this cancer.

Both anal and rectal cancer have shown a similar trend of increased incidence over time, particularly in women, which suggests a shared etiology. Furthermore, excess risk for rectal SCC occurs in HIV-positive and transplant patients compared to the general population, which is also observed in anal cancer. Since anal and rectal cancers share similar epidemiologic patterns and anatomic origin can be ambiguous, it has been suggested that rectal SCC could be misclassified as anal SCC. However, there is some evidence to suggest that rectal SCC can arise as a primary tumor. One study, using CAM5.2 cytokeratin as a marker for rectal epithelium, found similar prevalence of HPV16 in anal and rectal SCC, but CAM5.2 was restricted to rectal SCC. For simplicity, rectal SCC are often combined with anal cancer and are reported in national statistics of HPV-associated anal cancers. From a cancer surveillance perspective, this is done because of the overall low burden of disease and similar HPV type distribution profile, as demonstrated in this analysis.

Our findings can be interpreted in the context of the study’s limitations and strengths. We utilized a population-based strategy to obtain rectal and anal cancer cases from cancer registries in 3 US states. Despite the population-based efforts, the number of cases we were able to obtain was still relatively small, which limits the conclusions we are able to draw regarding the association between HPV and rectal SCC. Nonetheless, the high concordance and agreement between HPV status and p16 overexpression may lend support to the association.

Conclusion

CDC has traditionally combined rectal SCC with anal cancers for its count of HPV-associated cancers. This study confirms that for surveillance purposes it is justified to combine these 2 when describing HPV-associated cancers. The agreement between p16 and HPV status in both rectal and anal cancers lends additional support for the role of HPV in the etiology of these cancer types. Larger studies could be conducted to replicate these findings.
Table 3. Distribution of Single HPV Types in Rectal and Anal Cancer, CDC CRSSS, 2014–2015

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Rectal&lt;sup&gt;a&lt;/sup&gt; (n = 39)</th>
<th>Anal&lt;sup&gt;b&lt;/sup&gt; (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV16</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>HPV33</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>HPV6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>HPV18</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>HPV31</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HPV11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HPV45</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HPV52</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HPV58</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HPV73</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HPV55</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HPV67</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HPV42</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>HPV59</td>
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<td>2</td>
</tr>
<tr>
<td>HPV61</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>HPV66</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>HPV51</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HPV53</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HPV68</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HPV70</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HPV82</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HPV89</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; CRSSS, Cancer Registry Sentinel Surveillance System; HPV, human papillomavirus.
<sup>a</sup>Rectal cancer includes ICD-O-3 site code C20.9 and morphology codes 8050–8084 and 8120–8131.
<sup>b</sup>Anal cancer includes ICD-O-3 site codes C21.0–C21.8; morphology codes 8720–8790 (melanoma), 8800–8991 (sarcoma), 9050–9055 (mesothelioma), 9140 (Kaposi sarcoma), and 9590–9992 (leukemias/lymphomas) were excluded.
<sup>c</sup>Weighted percentages take into account sampling frame for age and race/ethnicity.
<sup>d</sup>Statistical testing performed with first order Rao-Scott $\chi^2$ statistics with $\alpha = .05$.
<sup>e</sup>Positive for any HPV type tested for.
<sup>f</sup>Positive for HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68.
<sup>g</sup>Positive for HPV types 6, 11, 26, 34, 40, 42, 43, 44, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 74, 81, 82, 83, 84, 89, or HPVIS39.
<sup>h</sup>Range of multiple types was 2–7.
<sup>i</sup>See methods section for further explanation of HPV type hierarchical classification.
<sup>j</sup>A total of 7 rectal and 4 anal cancer cases were HPV negative; 3 anal cancer cases were attributed to HPV6.
Raising the Bar

Leveraging Diversity to Create Synergy and Achieve Results

Michele Webb, CTR

We work in environments where there are a lot of differences. Typically, diversity is thought of as variations in social, cultural, or ethnic backgrounds. But it is also about the differing education, skills, and the clinical, professional, and personal experiences each member brings to the group. As a leader in your cancer program, how do you respond to diversity? Are you aware of it? Ignore it, run from it? Or, do you leverage it?

On October 5, 2017, Jerry Seinfeld appeared on Good Morning America, where he was asked about his success as one of the most famous comedians of all time. He went on to talk about his monologues and the art of delivering a punch line. He summed up his success by saying, “98% is the way you do it.”

Your understanding of diversity and the influence you have on the cancer program can also be summed up this way. Ninety-eight percent of your success as a leader will come from how you do it. Meaning, how you respond to the diversity around you, and how you communicate, build relationships, and leverage the strengths of the team, demonstrates your influence as a leader.

Leveraging diversity is about empowering people, understanding and valuing the differences each person brings. This creates a synergy that moves beyond working together to productive collaboration for a common cause. A successful leader will leverage diversity to increase effectiveness and ensure that each member of the team feels valued and is comfortable sharing their unique perceptions, insight, and knowledge to growing the cancer program.

Simply enforcing the requirements or regulations will not help you or your team perform at your best. Effective leaders know that the team is much more than a group. A group is simply a collection of individuals where each person is working towards his or her own goal, while a team is a collection of individuals working toward a common goal or vision. To achieve competitively charged results, you need to grow the work force from groups into teams that use everyone’s full potential and create synergy.

Here are 6 tips to help you leverage diversity, build synergy, and drive the performance of the team:

1. **Take time for self-reflection.** Understand your personal feelings about diversity and how it needs to be leveraged to accomplish your organization’s mission and vision. Do you appreciate each team member’s differences? Do you recognize their value? By understanding your own opinions and feelings, you will be prepared to lead with an open mind.

2. **Build rapport.** Invest time in learning about everyone on the team. You must get to know them in order to appreciate their strengths. Ask questions to learn about their background, education, and clinical, professional, and personal experiences. Discover what motivates them. By asking appropriate questions and sharing your own experiences, you will find a common ground and understand what makes each person uniquely different.

3. **Develop a 5-minute check-in habit.** All conversations with the team do not need to be task related. Check in periodically to see how each member is doing and ask them what you can do to help them. This act of caring for the team will make them feel that their contribution matters. It will encourage them to be comfortable sharing their thoughts and opinions and, eventually, using their best skills and becoming committed to the group.

4. **Encourage diverse conversation.** Leaders and teams fail when everyone is expected to think and act alike. You should encourage differences of opinion by challenging members of the team to think “outside the box.” Facilitate a comfortable and safe environment during meetings by asking team members for their opinions and then encouraging them to continue sharing their thoughts, even if they are different from others.

5. **Spend time together.** Take time to do something with individual members or the team. It is not always possible to plan an offsite retreat or social event outside of the workplace. But, you can look for brief moments to share a cup of coffee, meet for lunch, or spend 10 to 15 minutes to casually touch base. Encouraging community support or humanitarian activities, helping a coworker in need, or adopting a family or cause are also great ways to strengthen a team.

When you leverage the diversity in your group, you can balance the synergy between strategy and purpose. Any individual acting alone can accomplish a lot, but a team of people acting together in a well planned and unified force can accomplish so much more. Stephen Covey said, “Synergy is better than my way or your way. It’s our way.”
As a leader, focus your efforts on your relationships with the members of the team to recognize and understand their diverse strengths and experiences. Collaboratively leverage the resources to achieve the goals of the program. You will know synergy is happening when individual team members become “multipliers” and not “additions.” The team must operate together in synergy before high level results can be produced. By using this strategy, you can create a competitive edge and results-oriented cancer program that effectively serves the needs of your community and organization.

References

Michele is a cancer registry speaker and author who works with SCL Healthcare in Colorado and Montana. She is committed to helping others grow and expand their influence as leaders and mentors. Michele works remotely from her office in Manteca, California and enjoys quiet time with a good book and her 2 fur babies, Dolly and Cooper. Your feedback and comments are welcomed by email at michele@michelewebb.com.
COMPARING HUMAN PAPILLOMAVIRUS PREVALENCE IN RECTAL AND ANAL CANCER USING US CANCER REGISTRIES, 2014–2015

After reading this article and taking the quiz, the participants will be able to:

- Describe the relationship of HPV positivity in rectal and anal squamous cell carcinomas.
- Understand Centers for Disease Control and Prevention (CDC) groupings of rectal and anal squamous cell carcinomas.
- Describe the prevalence of HPV types in rectal and anal squamous cell carcinomas.

1. This study compared rectal and anal squamous cell carcinomas for which of the following?
   a) HPV prevalence
   b) HPV types
   c) Percentage of patients with rectal squamous cell carcinomas that received the HPV vaccine
   d) Both a and b
   e) All of the above

2. The data for the study originated in which states?
   a) Illinois, Iowa, Kentucky
   b) Illinois, Kentucky, Louisiana
   c) Iowa, Kentucky, Louisiana
   d) Indiana, Kentucky, Mississippi

3. Which types of cancer are included in this study?
   a) Rectal and colon squamous cell carcinoma
   b) Rectal and anal adenocarcinoma
   c) Rectal and anal melanoma
   d) Rectal and anal squamous cell carcinoma

4. In what 3 categories were the results grouped?
   a) HPV 16 positive, all other oncogenic HPV types except HPV 16, HPV negative
   b) HPV 16 positive, HPV 16 and another oncogenic types HPV positive, HPV negative
   c) HPV 16 positive, all other oncogenic types negative, HPV 16 negative
   d) HPV 16 positive, all other oncogenic types positive, HPV negative

5. Characteristics for HPV positive patients in this study differed by which of the following?
   a) Race
   b) SEER Summary Stage
   c) Sex
   d) Age
   e) None of the above

6. Which of the following is NOT a reason a case was excluded?
   a) Ineligible histology
   b) HPV typing was insufficient
   c) State of residence
   d) Age

7. What percentage of rectal cases had any HPV type positivity?
   a) 82.4%
   b) 90.6%
   c) 77.5%
   d) 12.9%

8. Which was the most common type of HPV in the samples studied?
   a) HPV 18
   b) HPV 16
   c) HPV 11
   d) HPV 56

9. This study helped demonstrate that HPV is a risk factor for which of the following?
   a) Anal squamous cell carcinoma but not rectal squamous cell carcinoma
   b) Rectal squamous cell carcinoma and anal squamous cell carcinoma
   c) Rectal melanoma and rectal squamous cell carcinoma
   d) Rectal lymphoma and anal squamous cell carcinoma

10. The CDC groups anal and rectal squamous cell carcinomas for counts of HPV-associated cancers. This study contends that:
    a) this is not accurate, as there is not concordance between HPV positivity and rectal and anal squamous cell carcinomas.
    b) this is accurate, as there is no statistically significant difference between the prevalence of HPV positivity in anal squamous cell carcinomas and rectal squamous cell carcinomas.
    c) this is accurate, even though the rectal squamous cell carcinomas show statistically significantly lower prevalence of HPV positivity.
    d) this is not accurate, as neither rectal squamous cell carcinomas nor anal squamous cell carcinomas show HPV positivity.

Purchase Quiz to Earn CE:
1. Go to http://www.cancerregistryeducation.org/jrm-quizzes
2. Select quiz and “Add to Cart” (You may be prompted to login using your NCRA login).
3. Continue through the checkout process.
4. Once purchase is complete, the quiz will load automatically into “My Learning Activities” page.
Reviewer acknowledgement: JRM gratefully acknowledges the individuals who have served as manuscript reviewers or have otherwise assisted in the review process during the past year. Their wise counsel and contributions to the Journal have been most valued.

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Bootle E, Canavan S, Plantz J. Overcoming Survivorship Care Plan (SCP) Barriers: Creative Staffing Solution. Fall;46(3):95-96.

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**African Cancer Registry Network**

**Anal**

### C

**Cancer**

**Cancer Registry**

**Cancer Risk**

**Cervical Intraepithelial Neoplasia**

**Cervical Precancer**

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**Data Sources**

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**Electronic Health Records**

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A Collaboration between Oncology Analytics and a Multidisciplinary Genitourinary Cancer Team for Data Collection: A Comprehensive Community Cancer Program’s Perspective


A Collaborative Assessment and Community Outreach Intervention of HPV-Type Cancers in the Local Region Utilizing Cancer Registry Data


Celebrating the 60th Anniversary of the American Joint Committee on Cancer

Macias TA, Justice D, Greene FL. Celebrating the 60th Anniversary of the American Joint Committee on Cancer. Summer;46(2):41-43.


Cost of Operating Population-Based Cancer Registries: Results from 4 Sub-Saharan African Countries


Essential TNM: Evaluation of a Training Exercise in Sub-Saharan Africa


Evaluating a Newly Developed System for Electronic Medical Records in Tanzania: An Example of the Experience in Low-Income Countries


Evaluating the Use of LAST 2-Tiered Nomenclature and Its Impact on Reporting Cervical Lesions in a Population-Based Cancer Registry


Fall 2019 Continuing Education Quiz

Vida C, BS, Mitchell S. Fall 2019 Continuing Education Quiz. Fall;46(3):107.

Health Behaviors and Other Risk Factors in Early Onset Colorectal Cancer: A Collaboration Among Northside Hospital Cancer Institute, Centers for Disease Control and Prevention, and National Association of Chronic Disease Directors


High Burden of Cancer Among Young Women Aged 20–49 Years


Holden Comprehensive Cancer Center: Oncology Registry Quality Management System and Waste Reduction


How Cancer Registry and Nurse Navigation Work Together to Improve Patient Care


How Do You Eat an Elephant?

How Do You Measure ACS–CoC Success?

Implementing a Systematic Quality Control Approach to Cancer Registry Data: A Quality Control Study on American Joint Committee on Cancer TNM Pathologic Staging for Cases with a Surgery Procedure Without Lymph Node Removal

Leveraging Diversity to Create Synergy and Achieve Results
Webb M. Leveraging Diversity to Create Synergy and Achieve Results. Winter;46(4):133-134.

Overcoming Survivorship Care Plan (SCP) Barriers: Creative Staffing Solution
Bootle E, Canavan S, Plantz J. Overcoming Survivorship Care Plan (SCP) Barriers: Creative Staffing Solution. Fall;46(3):95-96.

Quality Insiders: A Central Registry’s Quality Improvement Plan

Spring 2019 Continuing Education Quiz

Strategic Implementation of a Shared Service Cancer Registry Model in a Large National Health Care System

Summary of Veterans Health Administration Cancer Data Sources

Summer 2019 Continuing Education Quiz

The Impact of the Benign Brain Tumor Cancer Registries Amendment Act (Public Law 107-260) on Non-malignant Brain and Central Nervous System Tumor Incidence Trends

The Problem with Problems

Understanding Radiation Therapy—A Primer for Tumor Registrars
Apollo W. Understanding Radiation Therapy—A Primer for Tumor Registrars. Fall;46(3):91-94.

Using an Existing Birth Defects Surveillance Program to Enhance Surveillance Data on Stillbirths

Utility of Using Cancer Registry Data to Identify Patients for Tobacco Treatment Trials

Winter 2019 Continuing Education Quiz
National Cancer Registrars Association
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The Journal of Registry Management, official journal of the National Cancer Registrars Association (NCRA), announces a call for original manuscripts on registry methodology or research findings related to the 7 subjects listed below and related topics.

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