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Preventing injuries in female high school athletes: What are the barriers?

Injuries to female high school athletes are common and can result not only in less participation, but also may lead to long-term consequences that include chronic pain, decreased function, and a decrease in lifetime physical activity. Home-based Injury prevention programs may be effective in reducing these injuries, but research is limited. In this issue of *WMJ,* researchers explore barriers to compliance in a home-based injury prevention program.

Cover design by
Mary Kay Adams-Edgette

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EDITORIAL

ORIGINAL RESEARCH

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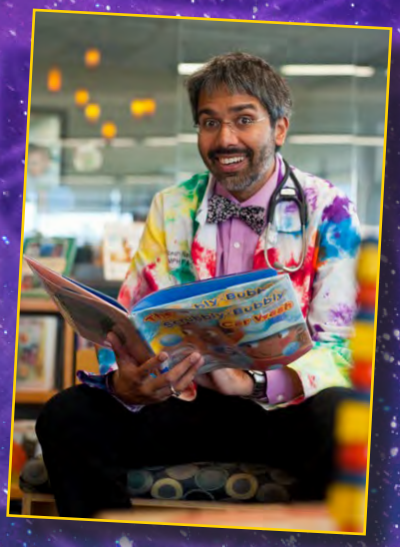

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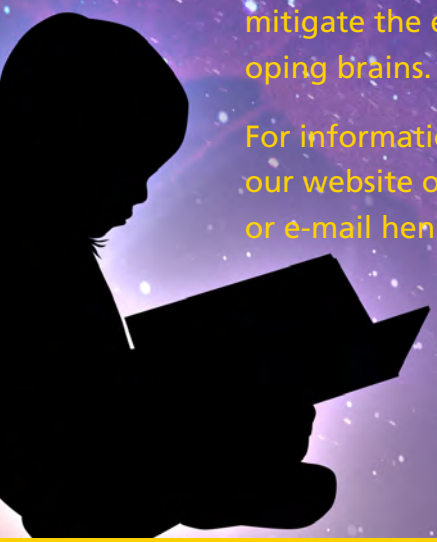

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Business or Busy-ness?

Editor's note: The following editorial was published in WMJ, *Volume 35, No. 1, p. 42, January 1936*

While this writer disclaims having reached the over-ripe age in which the Present is likely to be viewed astigmatically and the Past through rose-colored glasses he is among those who regret the passing of some of the amenities of the "horse and buggy days." Other Victorians have bemoaned the lost arts of conversation and letter-writing and we have much to say in the way of regret for the loss—even though it be doubtful if we have many to listen.

Doubtless conversation was not so interesting way-back-when, as we oldsters like to believe it was. For one thing, the wits of the nineties had no such stiff competition as "The New Yorker," which furnishes the present day "well-known clubman and man-about-town." Cheap newspapers and cheaper radio reception make old stuff, in a matter of seconds, of what in the good old days would have inspired a scribe to whittle a quill and scratch for hours on an epistle to a far-away relative or friend, later furnishing a motive for a series of neighborhood calls.

But be that all as it may, Modernity hasn't yet so successfully outmoded certain kinds of correspondence as some physicians, and many others, seem to think. "Saying it with flowers" doesn't say it as well as a personal card can be made to say it. Telepathy is too doubtful a medium to replace an unobstrusive and well-timed word of appreciation of a referred patient or other mark of favor. Indeed it would seem oftentimes to the cynically minded that about all that our various time-saving devices have been able to do for many of us, is to rob us of the leisure which professional gentlemen formerly had so abundantly and used so graciously. —H.E.D.

LETTER TO THE EDITOR

In Response to 'Rustproofing People'

We chuckled at the idea of rustproofing people and felt well-understood with Darold Treffert's story of his mother wanting to ride on the Harley and Dr T's own wish that he had attended fewer professional meetings and had taken flying lessons.[1]

There has to be a balance between reasonable measures for health and taking the time for some joy. But do doctors get caught up in rustproofing, excessive testing and health measures, partly to build practices, to avoid errors and complaints, and out of their own persistent deep fear of death? It's a proven fact that even a car with three coats of rustproofing will eventually go kaput. Thanks, Darold.

William Houghton, MD, and Mary Alice Houghton, MD, Milwaukee, Wisconsin

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Pre-exposure Prophylaxis in Primary Care–A New Era in HIV Prevention

Andrew E. Petroll, MD, MS; Rose A. Staden, APNP; Ryan P. Westergaard, MD, PhD

Pre-exposure prophylaxis (PrEP) is a powerful new prevention tool for those at substantial risk of acquiring HIV and can be used in combination with other HIV prevention methods. The antiretroviral single tablet combination containing emtricitabine and tenofovir (Truvada, Gilead Sciences Inc, Foster City, California) was approved by the Food and Drug Administration for this use in 2012 and formally recommended by the US Centers for Disease Control and Prevention (CDC) in May of 2014.[1] When taken as prescribed, PrEP provides 92% to 99% reduction in risk of acquiring HIV,[2] but it represents a significant paradigm shift in HIV prevention—the first time that a medication has been used to prevent HIV prior to exposure.

Because PrEP requires a prescription for Truvada, this new HIV prevention strategy lies squarely within the bounds of clinicians, and in most cases, beyond the scope of public health departments and community organizations that have traditionally worked to advance HIV prevention. While these groups can raise awareness and generate interest in the use of PrEP, its prescription will depend on clinicians.

Unfortunately, many clinicians are unfamiliar with PrEP and unaware of the recent CDC recommendation that all individuals at high risk of HIV should consider daily use of Truvada. To reach its full potential as an HIV prevention tool, clinicians must be aware of PrEP, be comfortable discussing it with patients, and either prescribe it or know where to refer interested patients. PrEP should be viewed as and offered like any other preventive health care service for high-risk patients.

Background

There are more than 8000 individuals estimated to be living with HIV in Wisconsin. On average, approximately 250 Wisconsin residents are diagnosed with HIV each year, a number that has remained steady for the last decade.[3] At the same time, the prevalence of HIV in African American men who have sex with men in Milwaukee is a staggering 32%, and the number of new diagnoses in young black men who have sex with men nearly tripled from 2004 to 2013. More than half of African American men who have sex with men newly diagnosed with HIV in 2014 were younger than 25 years old. HIV also continues to disproportionately affect gay and bisexual men of all races.

While it is estimated that conventional HIV prevention methods—such as behavioral risk reduction interventions, condom distribution, and HIV testing and counseling—have prevented millions of cases of HIV since the beginning of the epidemic, the unwavering rates of new infections both nationally and in Wisconsin suggest that additional strategies are needed. Recent research highlights the limitations of condom use as a primary HIV prevention strategy. CDC researchers retrospectively analyzed condom use and HIV infection from 2 different studies and found that among all men having anal sex, condoms were 70% effective for preventing HIV transmission with typical use.[4,5] The researchers also found that condom use was difficult to maintain over the long term, with just 16% of participants reporting 100% condom use with any anal sex over the 3-year period.

Safety and Efficacy of PrEP

Several large, international, randomized controlled trials have demonstrated that PrEP resulted in significant reductions in HIV incidence among men who have sex with men;[6] high-risk heterosexual adults;[7] including HIV serodiscordant couples;[8] and people who inject drugs.[9] A key lesson learned from these trials—and several others that failed to demonstrate effectiveness—is that, as with any prevention method, PrEP is highly dependent on adherence in order to effectively lower the risk of HIV acquisition. Compared to other HIV prevention strategies, daily oral chemoprophylaxis has several unique advantages. Condoms and other barrier protection methods require both that users anticipate sexual activity by having condoms readily available and that they successfully and properly use them. Reliance on individuals' ability to carry out condom use during sexual encounters demonstrates one of the weaknesses of this prevention method, as

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individuals may be distracted from a disease prevention mindset due to the aroused state created by sexual engagement. In addition, many individuals engage in sexual encounters while under the influence of alcohol or drugs, further reducing the likelihood of successful condom use. By contrast, successful use of PrEP is accomplished by taking one pill on a routine basis, outside of the emotionally charged atmosphere of a sexual encounter.

Implementation of PrEP

For individuals to realize the potential benefits of PrEP, 3 elements are required: (1) awareness of PrEP by individuals at risk for HIV infection; (2) awareness of PrEP by clinicians; and (3) familiarity among clinicians with prescribing PrEP or knowledge of where to refer patients for PrEP. Health care professionals need to be part of each of these steps so that they can raise awareness in patients who they feel could benefit from PrEP, but may be unaware of it, or to respond to individuals who themselves are requesting PrEP and are looking for a prescriber.

During the past 3 years, we began implementing PrEP within our 2 academic Infectious Disease/HIV clinics. As the largest providers of HIV-related care in our regions, we have seen a steady increase of patients seeking PrEP, but have been disturbed by the difficulty that many patients have had in finding our respective clinics. Many patients describe asking their primary care clinicians about PrEP, only to have been met with reactions that include discouragement, indifference, or lack of awareness. When they have been successfully linked to a PrEP provider, it has much more often been a result of their own initiative and persistence, rather than at the recommendation of their clinician.

Our experience suggests that a combination of low awareness of PrEP among clinicians and at-risk individuals has resulted in extremely low uptake in Wisconsin. We estimate that only approximately 100 individuals are currently taking PrEP in Wisconsin,[9] while estimates from other states in our region, Tennessee, and Ohio, range from 1000 to 2000 individuals.[10] In Wisconsin as in the United States overall, men who have sex with men, particularly African American men, experience extremely disproportionate HIV incidence and prevalence.[3] However, not every member of these demographic groups is at an elevated risk of HIV infection, and identifying those who could benefit most from PrEP requires knowledge of each patient's risk factors. Prior research indicates that most clinicians do not routinely ask about same-sex behaviors, and patients often do not disclose their sexual orientation without being asked.[11-13] Thus, identifying individuals appropriate for PrEP requires discussion of sexual and other HIV risk factors. While having such conversations may represent a change in practice for some clinicians, the potential benefits of PrEP when targeted to patients at high risk for HIV are large. (See Table for summary guide for PrEP use combining our clinics' experience and CDC guidelines.)

Concerns

Concerns have been raised about the cost of Truvada, which is more than $1300 per month.[14-16] However, when used as PrEP, Truvada is not necessarily intended to be taken for a lifetime, as is the costlier combination antiretroviral treatment for established HIV infection. Modeling studies suggest that the costs associated with PrEP are in line with other common preventive health measures when delivered to appropriate populations, and the required lab monitoring is relatively inexpensive when compared to the monitoring required for those who are HIV positive and living near normal life expectancies on antiretrovirals.

In general, insurance programs cover the cost of Truvada as PrEP, and patient assistance programs are available for many individuals with high copays or who are underinsured. In our experience, however, many patients seeking PrEP were unaware that they were eligible for government-sponsored insurance or subsidies for commercial health insurance, and there remain individuals who are ineligible for or unable to obtain health insurance. Thus, further action, such as Medicaid expansion or development of other funding mechanisms, is needed to provide PrEP to those at highest risk.

Some public health experts have raised concerns that PrEP will encourage unsafe sexual practices, including less condom use and therefore higher rates of sexually transmitted infections (STI). However, in our experience, some individuals seeking PrEP already have very poor condom use, which in some cases has actually improved after initiating PrEP. Other patients have consistent condom use, but are seeking additional protection. Further, the consequences of most STIs pale in comparison to HIV—both for individuals as well as the health care system—and once started on PrEP, patients are more engaged in the health care system, which creates opportunity for ongoing counseling regarding sexual health, STI screening, and HIV testing.

Sexually Transmitted Infections/ Sexual Health

PrEP should be implemented as a comprehensive HIV prevention strategy and should be used as an opportunity to promote sexual health and wellness, including complete STI testing. Despite CDC recommendations that sexually active gay and bisexual men be screened annually at all sites at risk for infection, we found low implementation of this testing and high rates of infection among patients seeking PrEP, prior to being seen in our clinics. Most of these patients were not aware of recommendations for testing of extra-genital sites and had only had urethral screening in the past. This is especially concerning because STIs are a known risk factor for HIV acquisition.

Since implementing PrEP in our clinics, we have found an alarming number of extra-genital STIs (rectum and pharynx) at initial clinic visits, the majority of which were asymptomatic. Notably, we have found no urethral infections through nucleic acid amplification testing of urine specimens, which is the approach to screening most widely adopted in primary care settings.

Conclusion

The need for improved HIV prevention measures is clear. PrEP provides an additional, safe and effective measure for those at highest risk. Unlike other prevention measures, PrEP

Table. Summary of Guidance for Pre-exposure Prophylaxis (PrEP) Use

Men Who Have Sex With Men	Heterosexual Women and Men	People Who Inject Drugs
Detecting Substantial Risk of Acquiring HIV Infection		
Sexual partner with HIV	Sexual partner with HIV	HIV-positive injecting partner
Recent bacterial STI	Recent bacterial STI	Sharing injection equipment
High number of sex partners	High number of sex partners	Recent drug treatment (but currently injecting)
History of inconsistent or no condom use	History of inconsistent or no condom use	
Commercial sex work	Commercial sex work	
	Lives in high-prevalence area or network	
Clinically Eligible		
Documented negative HIV test before prescribing PrEP		
No signs/symptoms of acute HIV infection		
Normal renal function (serum creatinine), no contraindicated medications		
Prescription		
Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90 day supply		
Follow-up visits at least every 3 months to provide: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment		
At 3 months and every 6 months after, assess renal function		
Every 6 months test for bacterial STIs		
Document hepatitis B virus infection and vaccinate non-immune individuals		
Other Services		
Do oral/rectal STI testing	Assess pregnancy intent Pregnancy test every 3months	Access to clean needles/syringes and drug treatment services

Abbreviation = sexually transmitted infections, STI.
Source: US Public Health Service.[1]

requires an encounter with a clinician, thereby providing an opportunity to optimize health for populations that may not otherwise see a need to access the health care system. Assessments for PrEP need to start in primary care and implementation should begin with support from infectious disease and HIV experts, with the eventual goal of implementation in primary care as clinician comfort grows, just like any other preventive health care service. PrEP provides a unique opportunity for health care professionals to make an impact on reducing the unacceptably high rate of new HIV diagnoses and the intolerable racial disparities that affect the people of Wisconsin.

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Behavior, Disparities, and Diagnostic Dilemmas

John J. Frey III, MD, Medical Editor

While HIV infection has been documented since the first report in *Morbidity and Mortality Weekly Report* in June, 1981, the story of its effects on the medical community is worth reviewing. With the newer generations of retroviral medications, people with HIV have been living with a chronic disease that remains a threat but—if they adhere to protocols—can be controlled. I have friends and former patients who have lived with HIV infections for over 30 years and are doing fine.[1] But the HIV story has been a different one in developed countries from that in the developing world. HIV and AIDS continue to devastate many countries in Africa and Asia where low-cost treatment and effective prevention still are not available to many. The emphasis for the World Health Organization's HIV programs has been education about high-risk behaviors, getting medications to those who are positive, and decreasing transmission to newborns.[2] In all cases, managing HIV infections and avoiding risks depend on patients to adhere to medication regimens and, as Petroll and his colleagues point out in this issue of the *WMJ,* it requires a change in physician behavior as well.[3]

Their commentary discusses ways that the practicing community can work with infectious disease specialists and public health to promote pre-exposure prophylaxis (PrEP) for patients who live in high-risk communities for HIV infection and who engage in unsafe behaviors. The reported success rates of prevention of HIV infection through the use of PrEP protocols in this population are truly remarkable. However, Petroll and colleagues point out that the awareness of the availability of PrEP among clinicians needs to be much higher and encouragement of high-risk patients should be much broader if society and patients are to realize the value from prevention. Although the drugs are expensive—what drugs aren't expensive these days—the long-term savings are substantial. We all have had experiences with the logic that should make high-risk patients decrease those risks, whether through safe sexual practices or needle exchanges, but we also know how human behavior can be unpredictable. We all look for ways to work with patients to increase adherence of all types, but human beings are fallible and as long as they are, adding a proven medication that will increase the likelihood of preventing the spread of HIV seems like a very wise thing to do.

> …part of our responsibility lies in educating patients and the public about the risks associated with the procedures we order and, in the process, re-educating ourselves.

Continuing Disparities

In the discussion of Wisconsin HIV prevalence and incidence data, Petroll and colleagues point out the continuing racial disparities in the state, with a disproportionate share of HIV prevalence and incidence in the African American community. Another article in this issue of the *WMJ* points out disparities in breast and colorectal cancer survival in the southeastern part of the state served by the Medical College of Wisconsin Cancer Center, with African Americans—again—seeing a significantly shorter survival rate than whites, and Latina women having shorter survival rates from breast cancer than white women.[4] In a second article, Foote and colleagues report high levels of many types of cancers in the American Indian/Alaska Native population of the state.[5] They show that American Indians who live in primary tribal areas are at greater risk of getting cancer than the overall American Indian population and that both groups are at higher risk than other non-Indian populations. Different populations are at risk in urban and rural communities but the data from these epidemiologic studies are compelling. These analyses should motivate the practicing community to look carefully at the environmental and behavioral components that we know are related to the development of cancer, work with communities on the local level to improve access to medical

care and education, work with public health to assess environmental safety, and find creative and community-specific ways to bring about behavioral changes in patients that focus on prevention. All of this is very hard work. But if Wisconsin is to meet its goals as a Healthy State, partnering with the most at-risk populations to find realistic solutions is essential.[6]

Just as the world is getting used to the idea of Ebola virus and its regional and international spread, viruses from Central and South America threaten to spread worldwide through travel. Climate change has amplified this dilemma by enabling vectors to spread to regions where they have not been endemic. The last decade has seen birds migrating to places where they rarely or never have been seen, but birds are the bellwethers for the more insidious spread of less beloved species. Much of the iatrogenic bacterial resistance that we have seen over the past 40 years is also regional and requires clinicians to look at patterns of prevalence by county and region. Munson and colleagues[7] include maps showing bacterial resistance in the state and there are different patterns for different bacteria. One wonders what led to the kinds of north/south differences in susceptibility to antibiotics that they found in their surveillance studies. Linking clinical, laboratory, and prescribing/pharmacy data, where possible, has the potential to offer changes in behavior by clinicians that could decrease resistant bacteria in communities. We have the data; now we need to use it.

Repplinger and colleagues studied the level of knowledge that patients who came to emergency departments showed when questioned about radiation exposures from CT and MRI exams. Not surprisingly, the authors found that understanding of the differences was quite low overall—even in patients who were health professionals. Therefore, part of our responsibility lies in educating patients and the public about the risks associated with the procedures we order and, in the process, re-educating ourselves.

Education can be difficult though, as illustrated by Thein-Nissenbaum and Brooks. Even when the clinicians developed innovative patient education methods—in this case an instructional DVD that could be watched on the patients' own time to help teenage women basketball players avoid injuries—they found that subjects' behavior didn't match the suggested guidelines.[8] One would think that giving teens something to watch on their computer screens would be an ideal method but, perhaps to no one's surprise, they got distracted and forgot.

Case Reports

The 3 case reports in this issue highlight diagnostic dilemmas facing clinicians. Garcia-Rodriguez discusses how what was feared to be a malignancy, to the relief of the patient and her physicians, turned out to be ectopic thyroid tissue with Hashimoto's thyroiditis mimicking metastatic disease.[9] Silva and Suarez remind us of the old axiom that, in a previously operated abdomen, one should think of adhesions as the source of almost any abdominal or pelvic complaint, even, in this case, of a patient with disabling urinary frequency.[10] And finally, Galbis-Reig reports on a case of Kratom addiction and withdrawal that should alert us, yet again, that when we sit with patients and go over medication use, we have to include everything a patient is taking, particularly in a world where unregulated herbal and over-the-counter "supplements" are available and widely used.[11] I had not heard of Kratom prior to receiving this article and since then have read of its wide availability and its potential for abuse and dependence. In our medication reviews, office staff always ask about prescription medication but rarely about a new or continuing "harmless" supplement. That needs to change.

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The High Burden of Cancer Among American Indians/ Alaska Natives in Wisconsin

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ABSTRACT

Objective: American Indians/Alaska Natives (AI/AN) who live in the Northern Plains, including Wisconsin, face disproportionate cancer disparities. This report examines cancer incidence and mortality based on residence in Contract Health Service Delivery Areas (CHSDA) to assess disparities between AIs/ANs and other racial populations in Wisconsin.

Methods: To improve identification of the AI/AN race, incidence data were linked with Indian Health Service (IHS) patient records. Analysis further focused on residents of IHS CHSDA counties. Age-adjusted cancer incidence and mortality rates (2007-2011) were calculated by sex and major cancer sites. AI/AN rates were analyzed for both statewide and CHSDA residency in comparison to statewide white rates and comparable national rates.

Results: In comparison with whites, AI/ANs in CHSDA counties had higher incidence rates of cervical (3.5 times), liver (3.2), lung (2.3), and kidney cancers (2.1), and higher mortality rates for liver (2.7), kidney (2.2) and lung (1.9) cancers. Although there were similar rates of prostate cancer incidence between the 2 populations, AI/ANs were 1.9 times more likely to die from the disease.

Conclusions: AI/AN individuals in Wisconsin CHDSA counties experience the highest cancer incidence rate of any racial group for both genders combined and for females. This population also has the highest mortality rate among all racial groups for both males and females. To meet the Wisconsin Comprehensive Cancer Control Plan 2015-2020 and Healthy People 2020 goals of lowering cancer incidence and mortality rates, the disproportionate cancer burden among AIs/ANs needs to be addressed.

BACKGROUND

Cancer Incidence among American Indians/Alaska Native

American Indians and Alaska Natives (AI/AN) face persistent disparities in health status and health care, including barriers to obtaining screening, health care, and treatment of cancer.[1]

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The Indian Health Service (IHS) is the primary vehicle through which the federal government provides health services to AI/ANs. However, limited funding for IHS and other barriers to care may result in limited access to health services. Several studies have reported dramatic regional variation in cancer incidence and mortality, especially higher rates of cancer in the Northern Plains states including Wisconsin.[2-5] *Cancer in North America 2007-2011*, a North American Association of Central Cancer Registries publication presenting data from 32 state cancer registries (meeting data standards and with sufficient AI/AN populations), shows that Wisconsin has the fifth highest incidence rates for males and third highest for females, as well as the highest lung cancer incidence rates for both males and females.[6]

Wisconsin Cancer Reporting System

The Wisconsin Cancer Reporting System (WCRS) is a population-based registry guided by a state statutory mandate to collect, manage, and analyze cancer data on Wisconsin residents. In 1994, WCRS became part of the National Program of Cancer Registries, funded by the Centers for Disease Control and Prevention. Over 30,000 newly diagnosed cancer cases were reported to WCRS for the most recent reportable diagnosis year.[7]

This report examines cancer incidence and mortality data based on residence in Contract Health Service Delivery Areas (CHSDA) to assess disparities between AI/AN, and other racial populations in Wisconsin. To meet the Wisconsin Comprehensive Cancer Control Plan 2015-2020 and Healthy People 2020 goals of lowering cancer incidence and mortality rates, the disproportionate cancer burden among American Indians needs to be addressed.

Figure 1.
Wisconsin Contract Health Service Delivery Area (CHSDA) Counties in the Department of Health Services Regions

METHODS

American Indians and Alaska Natives in Wisconsin

The US Census indicated the self-reported AI/AN 2010 population (single or in combination) in Wisconsin was 69,386.[8] For this study, SEER*Stat, statistical software from the National Cancer Institute (NCI), provided a bridged-race population estimate of 68,745 AI/ANs for the year 2011.[9] American Indians make up almost 100% of the AI/AN population in Wisconsin; only approximately 225 people in Wisconsin were identified as Alaska Natives.[10] The IHS (www.ihs.gov) provides health care to members of federally recognized American Indian tribes through directly administered federal facilities and by funding tribally operated health programs. Access to IHS-supported medical care is governed by set criteria most commonly related to enrollment in a federally recognized tribe. Specific criteria for enrollment in a federally recognized tribe are determined by each tribe. CHSDA counties are designated by IHS and contain or are adjacent to federally recognized tribal lands. In Wisconsin, there are 32 CHSDA counties in the state (Figure). There are 11 federally recognized tribes in Wisconsin, each with unique government, language, and health practices. These are the Bad River Band of Lake Superior Chippewa, Ho-Chunk Nation, Lac Courte Oreilles Band of Lake Superior Chippewa, Lac du Flambeau Band of Lake Superior Chippewa, Menominee Tribe of Wisconsin, Oneida Nation, Forest County Potawatomi, Red Cliff Band of Lake Superior Chippewa, St. Croix Chippewa, Sokaogon Chippewa (Mole Lake), and Stockbridge-Munsee.

Challenge of Data Collection

The collection of accurate data on cancer incidence among AI/ANs is hampered by misclassification of this population in cancer case reports.[11] To rectify misclassification and the tendency to report the AI/AN race as white, WCRS and other state cancer registries in the United States routinely link cancer case data to the IHS patient record registry.[12] In Wisconsin, of the 1005 invasive cancers diagnosed among AI/ANs in 2007-2011, approximately 15% were newly identified through the IHS linkage. The other method used to reduce misclassification is to restrict the selection of cases to residents in IHS CHSDA counties.[6,13] In Wisconsin, 62% of the 2011 AI/AN population of 68,745 reside in the 32 CHSDA counties. Of the 1005 reported cancer cases for this population during 2007-2011, 75% (761) were among residents of CHSDA counties. Nationally, 64% of the AI/AN population reside in 637 CHSDA counties, and linkage studies indicate more accurate race classification and higher proportions of this population in CHSDA counties.[7] Racial classifications for mortality data are ascertained from information recorded on death certificates and are not currently subject to the same corrective adjustments as incidence data (although NPCR-IHS linkage is currently underway and will be available in the future). Mortality data in this report are, therefore, potentially more underestimated than are incidence data.

Data Sources and Statistical Methods

Cancer cases diagnosed during 2007 through 2011 were selected from WCRS for Wisconsin and from SEER*Stat incidence files for the United States. Mortality data for deaths during 2002-2011 were drawn from SEER*Stat public use mortality files. Age-adjusted rates were calculated for all racial groups, including AI/ANs in CHSDA counties and the entire state. All rates, expressed per 100,000 population, were directly age adjusted to the 2000 United States standard population using SEER*Stat. Rates were calculated for all sites combined and for the 13 most frequent cancer incidence sites and 9 most common cancer mortality sites among AI/ANs.

Cancer registry incidence records (state and national) were linked with patient registration files from the IHS. Incidence data refer to invasive cancers, with the exception of the urinary blad-

Table 1. Cancer Incidence by Sex and Race, for Contract Health Service Delivery Areas (CHSDA), Wisconsin and United States

Wisconsin

	Male and Female				Male				Female			
	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count
All races	471.2	468.8	473.7	148,854	533.0	529.1	536.8	77,158	426.9	423.7	430.1	71,696
White	461.3	458.8	463.8	137,566	518.9	515.0	522.8	71,275	420.2	416.9	423.5	66,291
African American	544.1	530.0	558.4	6,512	680.8	655.6	706.7	3,501	448.6	431.9	465.6	3,011
AI/AN, CHSDA	576.3	531.8	623.3	761	600.2	525.2	681.9	340	570.5	513.8	631.4	421
AI/AN, Total	483.4	450.6	517.8	1,005	503.7	449.3	562.1	459	476.1	434.1	520.9	546
Asian/Pacific Islander	291.8	271.7	312.8	976	311.3	277.1	348.1	410	288.0	262.8	314.8	566

United States

	Male and Female				Male				Female			
	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count
All races	460.4	459.7	461	2,001,481	529.4	528.4	530.5	1,033,837	411.3	410.5	412.2	967,644
White	468.9	468.2	469.6	1,628,476	532.1	530.9	533.2	840,730	424.4	423.4	425.3	787,746
African American	480.8	478.6	482.9	208,379	600.9	597.0	604.7	110,040	398.8	396.3	401.4	98,339
AI/AN, CHSDA	319.3	311.8	326.9	7,934	348.1	335.9	360.7	3,774	301.9	292.4	311.7	4,160
AI/AN, Total	235.1	230.2	240.1	10,362	259.3	251.3	267.5	4,991	219.9	213.7	226.2	5,371
Asian/Pacific Islander	306.7	304.9	308.4	121,493	331.0	328.2	333.9	55,972	293.0	290.7	295.3	65,521

Data are for years 2007-2011. Rates are per 100,000 population and age-adjusted to the 2000 U.S. standard population.
Abbreviations: AI/AN, American Indians/Alaska Natives.
Sources: Wisconsin Cancer Reporting System, Office of Health Information, Division of Public Health, Department of Health Services, and Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat. US Incidence - SEER 18 Regs Research Data, Nov 2013 Sub (2000-2011). SEER counts are based on data from 18 registries to represent a national estimate. Data accessed November, 2014.

Table 2. Cancer Mortality by Sex and Race, for Contract Health Services Delivery Areas (CHSDA), Wisconsin and United States

Wisconsin

	Male and Female				Male				Female			
	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count
All races	174.6	173.2	176.1	55,901	212.6	210.1	215.1	29,278	148.4	146.6	150.3	26,623
White	172.6	171.1	174.1	52,731	210.0	207.5	212.5	27,638	146.8	144.9	148.6	25,093
African American	236.0	226.2	246.1	2,508	296.0	278.1	314.6	1,315	195.7	184.2	207.6	1,193
AI/AN, CHSDA	252.2	220.0	287.3	270	320.2	257.3	391.7	139	215.1	177.7	257.3	131
AI/AN, Total	216.8	193.0	242.6	371	262.4	218.0	312.0	187	191.4	162.9	223.0	184
Asian/Pacific Islander	103.1	90.6	116.6	291	120.2	98.2	144.9	138	93.1	78.1	109.8	153

United States

	Male and Female				Male				Female			
	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count	Rate	Lower CI	Upper CI	Count
All races	173.8	173.6	174.0	2,847,364	211.6	211.3	212.0	1,488,124	147.4	147.2	147.7	1,359,240
White	173.3	173.1	173.5	2,440,835	209.8	209.4	210.1	1,278,795	147.5	147.3	147.8	1,162,040
African American	206.4	205.7	207.1	325,388	269.3	267.9	270.7	167,469	169.0	168.2	169.9	157,919
AI/AN, CHSDA	158.0	154.7	161.4	9,743	190.0	184.2	196.0	5,081	135.2	131.2	139.3	4,662
AI/AN, Total	120.0	117.8	122.2	13,770	145.2	141.4	149.0	7,252	102.1	99.5	104.8	6,518
Asian/Pacific Islander	107.8	107.0	108.6	67,371	131.0	129.6	132.5	34,608	91.5	90.4	92.5	32,763

Data are for years 2007-2011. Rates are per 100,000 population and age-adjusted to the 2000 U.S. standard population.
Abbreviation: AI/AN, American Indians/Alaska Natives.
Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Mortality - All COD, Aggregated With State, Total U.S. (1990-2011), National Cancer Institute, released July 2014. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

der (bladder), which includes in situ cancers. Data for the primary cancer site and histology were coded according to the International Classification of Diseases for Oncology (ICD-O-3) edition in use at the time of diagnosis, and then categorized according to SEER site groups.[14] The underlying cause of death was coded according to the International Classification of Diseases, 10th Revision (ICD-10).[15] Mortality data are not currently linked to IHS records. Consistent with previous practice, this report shows the standard mortality rates

Table 3. Cancer Incidence for Whites and CHSDA American Indians/Alaska Natives, Wisconsin

	White		AI/AN		AI/AN/White
Cancer Site	Rate	Count	Rate	Count	Rate Ratio
All sites	461.3	137,566	576.3[a]	761	1.2
Lung and bronchus	59.3	17,803	133.7[a]	150	2.3
Prostate	134.7	19,406	132.3	74	1.0
Breast	124.9	19,415	118.5	95	0.9
Colon and rectum	40.6	12,252	#58.2	72	1.4
Kidney and renal pelvis	16.2	4,807	#34.4	50	2.1
Non-Hodgkin Lymphoma	20.6	6,111	23.8	26	1.1
Oral cavity and pharynx	11.1	3,357	#19.5	29	1.8
Cervix uteri	5.4	719	#18.9	17	3.5
Liver and intrahepatic bile duct	5.2	1,585	#16.6	19	3.2
Ovary	13.0	2,026	16.4	13	1.3
Leukemia	15.9	4,635	16.1	22	1.0
Pancreas	12.2	3,703	13.9	15	1.1
Uterus	28.1	4,537	26.6	24	0.9

Data are for years 2007-2011. Rates are per 100,000 and age-adjusted to the 2000 US standard population.
[a] The rate ratio indicates that the rate is significantly different than the rate for whites ($P < 0.05$).
Abbreviations: CHSDA, Contract Health Service Delivery Area; AI/AN, American Indian/Alaska Natives (CHSDA counties).
Source: Wisconsin Cancer Reporting System, Office of Health Information, Division of Public Health, Department of Health Services.

Table 4. Cancer Mortality for Whites and CHSDA American Indians/Alaska Natives, Wisconsin

	White		AI/AN		AI/AN/White
Cancer Site	Rate	Count	Rate	Count	Rate Ratio
All malignant cancers	177.0	104,173	257.5[a]	510	1.5
Lung and bronchus	46.7	27,178	87.7[a]	174	1.9
Colon and rectum	15.7	9,396	23.8[a]	41	1.5
Breast	22.0	7,174	27.6	32	1.2
Prostate	25.7	5,999	45.8[a]	19	1.8
Liver and intrahepatic bile duct	4.6	2,692	12.6[a]	27	2.7
Pancreas	11.1	6,526	11.2	24	1.0
Kidney and renal pelvis	4.4	2,606	9.8[a]	22	2.2
Non-Hodgkin Lymphoma	7.2	4,281	9.0	16	1.2
Leukemia	8.1	4,744	8.1	15	1.0

Data are for years 2002-2011. Rates are per 100,000 and age-adjusted to the 2000 US standard population.
[a] The rate ratio indicates that the rate is significantly different than the rate for whites ($P < 0.05$).
Abbreviations: CHSDA, Contract Health Service Delivery Area; AI/AN, American Indian/Alaska Natives (CHSDA counties).
Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Mortality - All COD, Aggregated With State, Total U.S. (1990-2011), National Cancer Institute, released July 2014. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

as reported from death certificates, and thus are potentially subject to misclassification and underreporting.

Wisconsin's relatively small American Indian population limits mortality analyses to major sites, and the small number of cancer cases requires aggregation for confidentiality restrictions and acceptable statistical reliability. Accordingly, incidence data were aggregated by the most recent 5-year interval. Mortality data for all cancers was reported by a 5-year interval, but mortality data by site required a 10-year interval. Using age-adjusted incidence and mortality rates, we calculated standardized rate ratios for AI/ANs using whites for the comparison. Rate ratios (RRs) were calculated using SEER*Stat, and 95% confidence intervals (CIs) for age-adjusted rates and RRs were calculated based on statistical methods described by Tiwari et al.[16]

RESULTS

During 2007-2011, the likelihood of being diagnosed with cancer varied greatly by race as shown in Table 1. In Wisconsin, incidence rates for AI/ANs in CHSDA counties were approximately 19% higher for both sexes than when calculated for this population statewide. During that period, 1005 AI/AN cancer cases were diagnosed in Wisconsin with an incidence rate of 483.4 (per 100,000), and 761 cases were diagnosed in CHSDA counties, with an incidence rate of 576.3. The cancer incidence rate for AI/ANs in CHSDA counties was the highest of any racial group for both genders combined and females. For AI/AN males, the rate was second highest to African American males, but the difference was not statistically significant.

Cancer incidence rates among all AI/ANs in Wisconsin were approximately twice as high as national rates for total cases and 80% higher for CHSDA cases. Comparing Wisconsin CHSDA and non-CHSDA counties, the incidence rate for whites in CHSDA counties was 459.7 (CI, 455.6-463.7) and, for non-CHSDA counties, 470.3 (CI, 467.2-473.5). The incidence rate for AI/ANs in CHSDA counties was 576.3 (CI, 531.8-623.3), but 308.3 for AI/ANs in non-CHSDA counties (CI, 256.8-355.2). Data are not shown for this comparison.

Table 2 shows the risk of dying from cancer differed markedly among racial groups in Wisconsin, which also is true nationally. The age-adjusted mortality rate for AI/AN people in Wisconsin was approximately 16% higher for residents of CHSDA counties than statewide, but this difference is not statistically significant. AI/ANs living in CHSDA counties in Wisconsin had the highest mortality rates among all racial groups for the years analyzed—for men, women and both sexes combined. Nationally the comparable mortality rates for AI/ANs (CHSDA) were lower than rates for whites and African Americans.

Tables 3 and 4 present Wisconsin cancer incidence and mortality rates by site for whites statewide and AI/ANs in CHSDA coun-

ties. All remaining results refer to CHSDA counties only. Rates for all cancer combined and the most common cancers are presented. AI/ANs in Wisconsin had statistically significantly higher incidence rates of all cancer sites combined, lung, colorectal, kidney, oropharyngeal, liver, and cervical cancers than whites. The degree of disparity varied by site; AI/ANs were twice as likely to have lung and kidney cancer, as shown in Table 3. Cervical cancer and liver cancers were 3 times more common, and oral cancer was almost twice as common. They also had similar incidence rates of breast and prostate cancers compared with whites.

Table 4 shows that this population had a 50% higher mortality rate for all cancers combined compared to whites. They experienced equal or higher mortality rates for all cancer sites shown and were approximately twice as likely to die from cancers of the lung or kidney, and 2.7 times as likely to die from liver cancer—the site with the largest disparity.

DISCUSSION

Shift in Surveillance Data

Nationwide, AI/ANs historically have been reported as having lower rates of cancer than other racial groups, except for Asian/Pacific Islanders, but according to various state and national data the reported rates have been increasing in recent years.[6,13,17] The rates may have been underreported because of past misclassifications and flaws in collecting cancer data. WCRS and many other state cancer registries currently link data with IHS records and use data from CHSDA counties as the current "gold standard" in data collection for this racial group.[7]

High Cancer Rates in Northern Plains

Previous research has identified cancer disparities among AI/AN in the Northern Plains region. In the Northern Plains, AI/ANs have a higher cancer incidence rate than do whites, and the highest incidence and mortality rates compared with AI/ANs in other regions of the United States. Northern Plains AI/ANs have an increased risk of developing and dying from lung, colorectal, breast, cervical, and prostate cancers.[2-5,16] Some of this variation may be due to differences in social and environmental factors, which in turn lead to differences in alcohol use, obesity, and smoking—risk factors found to be more prevalent in the Northern Plains region.[2,16]

Behavior Risk Factors

Behavior Risk Factor Surveillance (BRFS) data for Wisconsin have shown smoking prevalence among AI/ANs as high as 40% to 50%, although more recent studies found lower rates closer to 30%.[18,19] Moreover, compared to other racial/ethnic groups, AI/AN high school students had the highest prevalence of tobacco use during 2008-2012 (40%), although lower than the prevalence for 2000-2004 years (55%).[20] Ceremonial use of tobacco is in the context of traditional American Indian culture, but the health consequences of commercial tobacco use are well known, and tribal communities are working to reduce smoking.[21] In addition to lung cancer, smoking is a significant factor in cancers of the throat, mouth, nasal cavity, esophagus, stomach, pancreas, kidney, bladder, and cervix, as well as acute myeloid leukemia.[22] The 2013 Wisconsin BRFS estimate for obesity prevalence among AI/ANs was 38%[19]. The 2011-2013 Youth Risk Behavior Survey data show a 51% prevalence for drinking among AI/AN high school students, higher than other racial/ethnic groups of that age.[23]

Socioeconomic Risk Factors

Individual behaviors alone do not explain differences in health status between groups. Healthy People 2020 documents the leading social determinants of health and describes a range of personal, social, economic, and environmental factors that contribute to individual and population health. Many AI/ANs live in communities that are economically depressed and have lower levels of insurance coverage.[24] In Wisconsin, AI/ANs have a higher poverty rate than whites (28% and 10%, respectively) and a lower employment rate (67% and 83%, respectively).[25] They generally have a lower prevalence of screening for colorectal, breast, and cervical cancer, which largely determine the stage at diagnosis, treatment options and, in some cases, survival and clinical outcomes.[26,27] The National Cancer Institute reports that AI/ANs have the lowest national 5-year survival rate for all cancers combined among all races.[28]

Limitations

Results of this analysis should be interpreted within the context of certain limitations. WCRS is a passive system of data collection in that all data are reported by medical facilities throughout the state. The original quality of data rests on proficiency at the reporting facilities. Final incidence data from WCRS are compilations of reported case submissions, subject to state and national standard edits, consolidated if reported from multiple sources, and linked to IHS registration lists. The SEER*Stat bridged-race population estimates used as the rate denominator are based on the self-reported race information from the US Census. However, the rate numerator is based on secondary identification of race reported to WCRS from facility reporters and from linkage to IHS files. The different methods of racial identification may have unknown inconsistencies. The data linkage fails to correct those AI/AN cases misclassified in WCRS records and not enrolled in the IHS files. The relatively small AI/AN population in Wisconsin limits analysis ,and caution is warranted in highly specialized interpretations of the limited data. Despite limitations, the magnitude of the disparity, continuity of rates over many years, and the consistency with rates in other states in the Northern Plains region, indicate the surveillance data are valid and useful for data-driven public health planning, interventions, and policy development.

CONCLUSIONS AND NEXT STEPS

The results of this study confirm the need for increased efforts to address individual-level behavior changes, as well as policy and system-level changes that promote healthy lifestyles and increased access to cancer screening and treatment.

Cancer control has become a priority for American Indian tribes in Wisconsin, as cancer surveillance data have revealed high rates of cancers. Cancer control programs such as the Spirit of EAGLES[29] have been initiated to increase awareness within AI/AN communities to better address the prevention, screening, and treatment priorities of Wisconsin tribes. Coalitions such as the Wisconsin Native American Tobacco Network[30] collaborate with AI/AN communities to promote cessation, prevent commercial tobacco abuse, and and reduce second-hand smoke exposure. Progress has been made: High school youth smoking rates have decreased, but more needs to be done. Expanded preventive programs (smoking cessation, nutritional and activity programs) and increased access to screening (Pap screening, computed tomography (CT) lung cancer screening, prostate cancer screening) suggest that current rates of cancer mortality could decrease within a generation.

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Breast and Colorectal Cancer Survival Disparities in Southeastern Wisconsin

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ABSTRACT

Background: Cancer health disparities by race, ethnicity, socioeconomic status, and geography are a top public health priority. Breast and colorectal cancer, in particular, have been shown to exhibit significant disparities and contribute a large proportion of morbidity and mortality from cancer. In addition, breast and colorectal cancer offer targets for prevention and control, including nutrition, physical activity, screening, and effective treatments to prolong and enhance the quality of survival. However, despite the investment of significant time and resources over many years, breast and colorectal cancer disparities persist, and in some cases, may be growing.

Methods: This paper examines breast and colorectal cancer survival disparities in an 8-county region in southeastern Wisconsin, including the City of Milwaukee. Cox proportional hazards models were used to examine survival trends, and a new adaptation of adaptive spatial filtering—a disease mapping method—was used to examine spatial patterns of survival.

Results: Disparities by race and ethnicity are revealed, and spatial analyses identify specific areas within the study region that have lower than expected survival rates.

Conclusions: Cancer control efforts in southeastern Wisconsin should focus on black/African American and Hispanic/Latina women to reduce breast cancer survival disparities, and black/African American populations to reduce colorectal cancer disparities. Evidence indicates that targeted interventions may be needed to serve populations in the Milwaukee and Kenosha metropolitan areas, as well as areas of Walworth, Ozaukee, and Waukesha counties.

INTRODUCTION

Approximately 30,000 Wisconsin residents are diagnosed with cancer each year, and over 11,000 die from cancer.[1] Cancer health disparities by race, ethnicity, socioeconomic status, and geography are a top public health priority. Breast and colorectal cancer, in particular, have been shown to exhibit significant racial and ethnic disparities, contribute a large proportion of morbidity and mortality from cancer, and offer targets for prevention and control, including nutrition, physical activity, screening, and effective treatments to prolong and enhance the quality of survival. However, despite the investment of significant time and resources over many years, breast and colorectal cancer disparities persist and in some cases may be growing.

African Americans in Wisconsin have higher age-adjusted incidence and mortality rates per 100,000 from colorectal cancer,[1] and although African American women are less likely to be diagnosed with breast cancer than white women in Wisconsin, they are more likely to succumb to the disease.[2] Nearly 90% of African Americans in Wisconsin live in southeastern Wisconsin counties, with almost 70% living in Milwaukee County, mostly in the City of Milwaukee.[3]

Milwaukee has been called one of the most segregated cities in America.[4] Local historian John Gurda has examined the process by which segregation and urban decline took root in Milwaukee,[5] describing the processes of migration and disinvestment in Milwaukee's urban core. Disinvestment was accompanied by decreasing home values and discriminatory housing policies that resulted in long-term entrenched poverty and residential racial segregation in the city. Interconnections among race, place, and socioeconomic status are now well established in Milwaukee, and spatial patterns of socioeconomic status are correlated with a range of adverse disease outcomes.[6-8]

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Table. Multivariate Cox Proportional Hazards Regression (HR) Models Predicting All Causes and Cancer Specific Breast and Colorectal Cancer Survival

	Breast (All Causes)	Breast (Cancer Specific)	Colorectal (All Causes)	Colorectal (Cancer Specific)
Race and Ethnicity	**HR**	**HR**	**HR**	**HR**
White	Referent	Referent	Referent	Referent
Black/African American	1.55[a]	1.55[a]	1.21[a]	1.18[a]
Hispanic/Latino	1.60[a]	1.54[a]	0.75	0.83
American Indian/Alaska Native	1.40	0.85	1.17	1.41
Asian/Pacific Islander	1.23	1.08	1.23	1.15
Other/Unknown	0.85	0.72	1.90[a]	2.01[a]

[a] *P*-value < 0.05.

To reduce the cancer burden in Wisconsin and reduce cancer disparities, a focus on southeastern Wisconsin is of clear importance. Because of the availability of screening tests and the advantage of early stage diagnosis, as well as the availability of therapies to lengthen survival, this proposed work focuses on disparities in breast and colorectal cancer survival in southeastern Wisconsin to provide actionable evidence to guide future cancer control efforts in the region.

METHODS

Study Area

The study area is defined as 8 counties in southeastern Wisconsin (Milwaukee, Jefferson, Kenosha, Ozaukee, Racine, Walworth, Washington, and Waukesha counties). Overall, the population of this area is 14% black/African American, 10% Hispanic/Latino, 72% white, and ~5% other minorities. The City of Milwaukee is the metropolitan center of this region with approximately 595,000 residents, of whom 39% are black/African American, 17% are Hispanic/Latino, and 38% are white, in addition to other racial and ethnic minority populations.

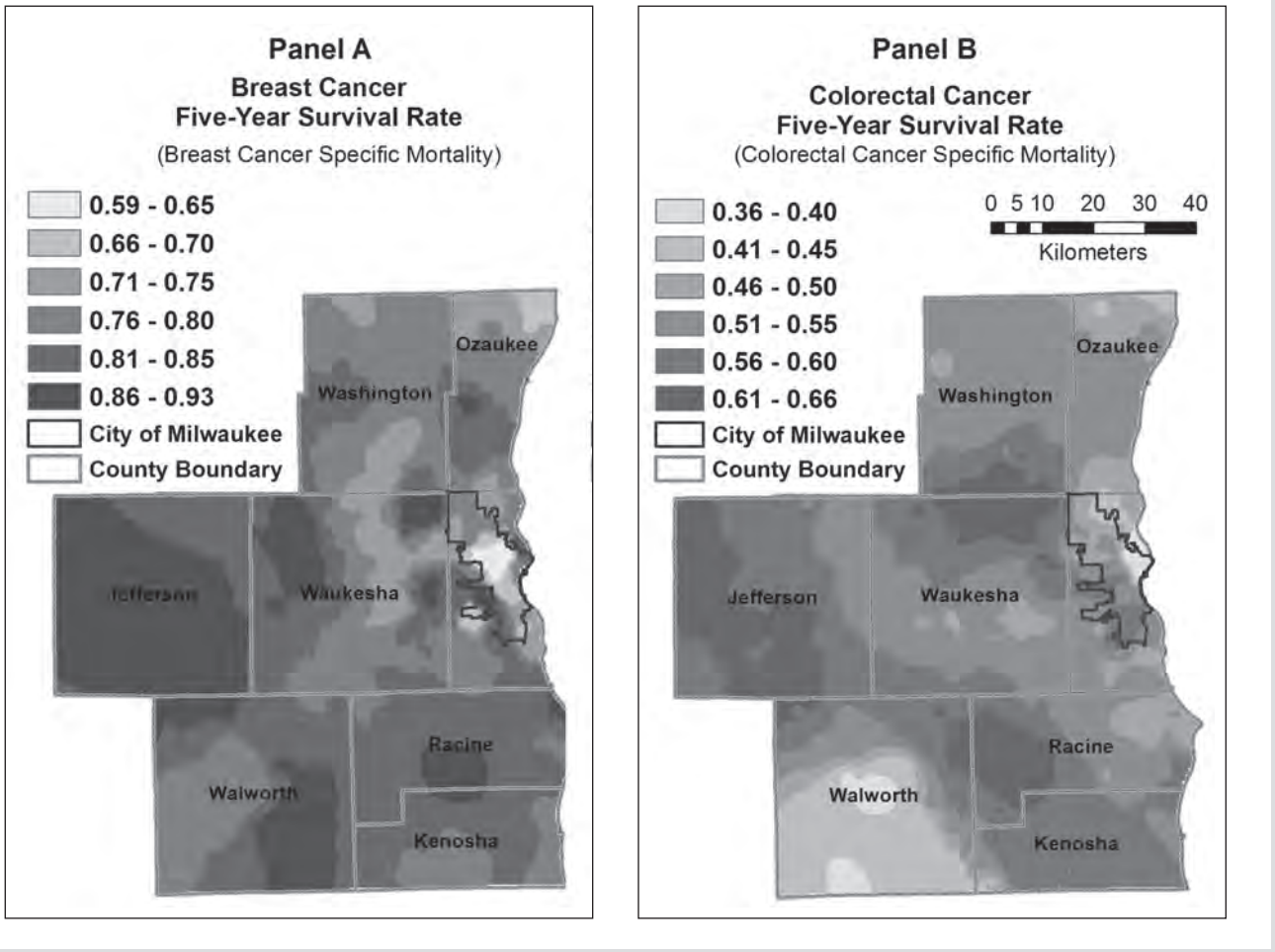
Data and Analysis

Incidence data were obtained from the Wisconsin Cancer Reporting System (WCRS) for the years 2002-2011 for invasive breast and colorectal cancers for the study area. This study was authorized by the institutional review board and approved by the Wisconsin Department of Health Services (DHS) Research Review Board for the release of cancer data for the purpose of cancer prevention and control as defined in Wis Stat. 255.04(3)(c). WCRS is a population-based tumor registry in the Office of Health Informatics, Division of Public Health, in DHS. Guided by statutory mandate, it collects, manages, and analyzes cancer data on Wisconsin residents newly diagnosed with pre-invasive and invasive cancers.[9] Cases are reported by hospitals, physicians, and clinics, including important data such as demographic data, tumor characteristics, and treatment. WCRS registry records are linked with the Wisconsin Vital Records resident death file on a yearly basis, providing the date and cause of death. Those registry records not matched to the Wisconsin resident death file are then sent to the National Center for Health Statistics for National Death Index (NDI) linkage. Records linked to the NDI also include the date and cause of death.

ICD-O-3 codes were used to define breast and colorectal cancer, based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) coding guidelines for breast and colorectal cancers. Two subsets were created to represent all individuals who had an initial diagnosis of invasive breast (n = 11,411) or colorectal (n = 7286) cancer during 2002-2011. Descriptive statistics were calculated for each subset, Cox proportional hazards models were used to examine survival trends by race and ethnicity (white/Caucasian, black/African American, Hispanic/Latino, Indigenous, Asian Pacific Islander, Other/Unknown) while adjusting for age (5-year age groups), stage of disease at diagnosis (localized, regional, distant, and unstaged, based on SEER Summary 2000 stage), marital status (single, married, separated, divorced, widowed, unknown) and sex (for colorectal cancer only). Analyses examined both overall mortality and cancer-specific mortality.

Geographic identifiers available from WCRS included the ZIP code and county of residence at the time of diagnosis. Records were geocoded by project staff to ZIP Code Tabulation Area (ZCTA) centers.[10] A new adaptation of adaptive spatial filtering—a disease mapping method—was used to examine spatial patterns of survival. Adaptive spatial filtering (ASF)[11-16] is a disease mapping method designed to overcome problems with traditional disease maps that rely on administrative boundaries (eg, county), such as the small numbers problem and the modifiable areal unit problem.[17-20] In ASF, a grid is placed over the study area, and for each grid point, a rate is calculated by using a circular filter that expands, based on a threshold specified by the user, to obtain data from multiple locations until it obtains enough observations to calculate a stable rate. The result is a map that displays disease rates as a continuous surface. Until recently, the ASF method only had been used to calculate incidence and mortality rates using age standardization procedures. Here, we extend this method to present 5-year survival rates continuously across geographic space. Cancer data were aggregated by ZIP code, and Census Block Group centroids were employed as the analysis grid. Data from counties bordering the study area was incorporated into these spatial analyses to mitigate the influence of border effects on resultant spatial patterns; maps were cropped to the study area boundary.

Figure 1. Spatial Patterns of Breast and Colorectal Cancer 5-Year Survival (Cancer-Specific Mortality)



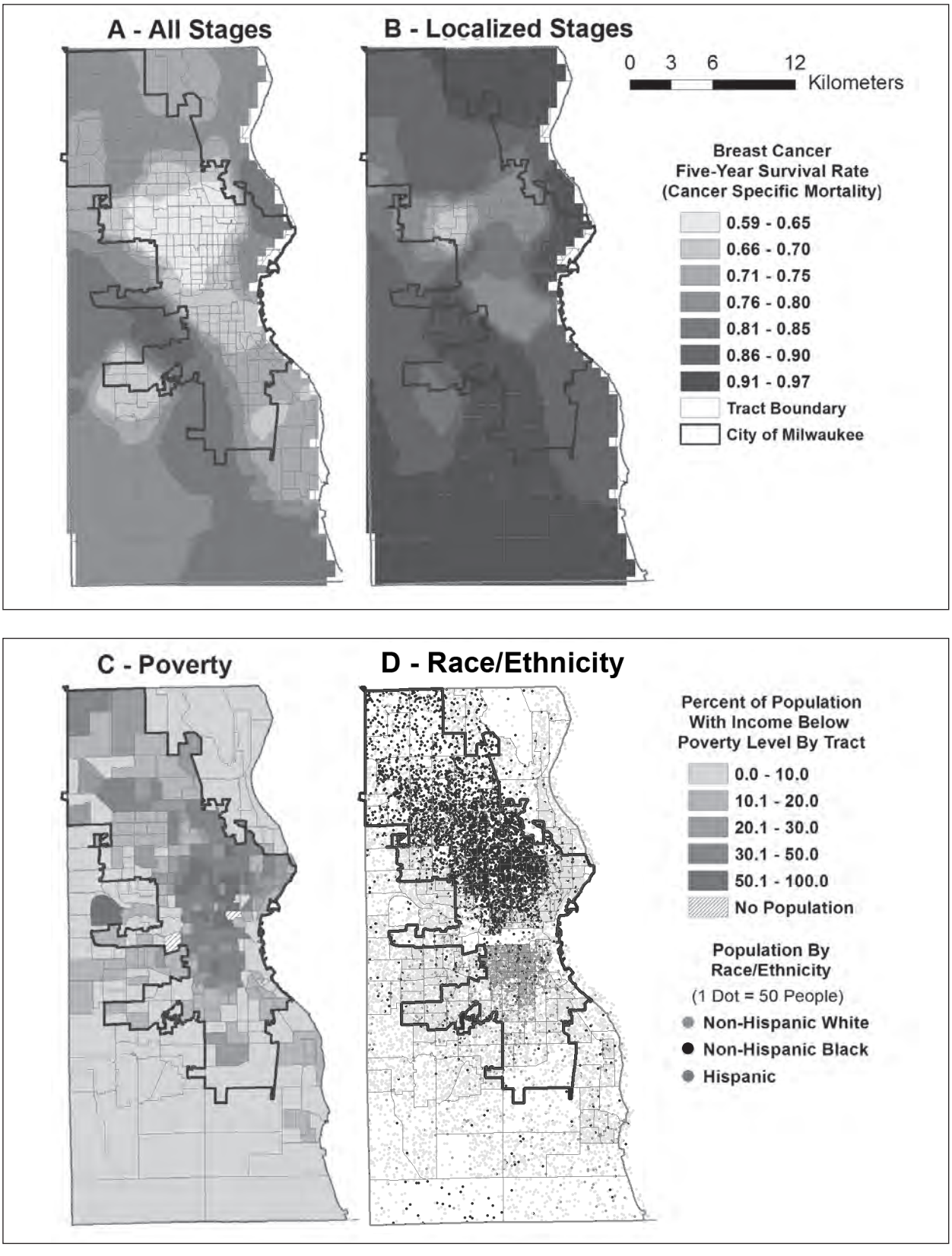
RESULTS

Kaplan Meier analyses revealed distinct disparities by race and ethnicity in survival post breast cancer diagnosis. Black women experienced the poorest survival, and white women experienced the best survival. Odds ratios (OR) for race and ethnicity resulting from the Cox proportional hazards analyses for both overall mortality and cancer-specific mortality for breast and colorectal cancer are presented in the Table. Black/African American individuals experience poorer survival than white people for all outcomes examined, with higher hazard ratios for breast cancer than colorectal cancer. Hispanic/Latina women experienced significantly poorer breast cancer survival than white women. Unsurprisingly, older age and later stage at diagnosis were associated with poorer survival for both breast and colorectal cancer. Compared to single individuals, married individuals experienced higher survival for both breast and colorectal cancer, while separated individuals experienced poorer colorectal cancer-specific mortality. Widowed individuals experienced more favorable all-cause mortality when compared to single individuals. Men diagnosed with colorectal cancer experienced poorer all-cause and colorectal cancer-specific mortality, when compared to women.

Figure 1 displays the 5-year survival rates for breast and colorectal cancer as a continuously defined disease surface. Rates represent the proportion of individuals in each local area who are still alive 5 years after diagnosis. Category breaks are set at 5% intervals. Clear spatial patterns emerge, highlighting poorer breast cancer survival rates in the Milwaukee metropolitan area, and colorectal cancer survival disparities in Walworth County and some areas in and around Milwaukee. Areas of Ozaukee and Waukesha counties also exhibit lower survival rates.

To enhance interpretation, Figure 2 presents the 5-year survival rate map for breast cancer in Milwaukee County (Panel A), along with a five-year survival rate map for localized (early stage) breast cancers only (Panel B), and maps that use US Census data to illustrate the poverty rate (Panel C) and the racial and ethnic distribution of populations throughout Milwaukee County (Panel D).

Figure 2. Breast Cancer Survival (5-Year Survival and 5-Year Survival for Women with Localized Tumors, Cancer-Specific Mortality), Poverty and Race/Ethnicity in Milwaukee County



CONCLUSIONS

This study revealed significant cancer survival disparities by race, ethnicity, sex, and geography in southeastern Wisconsin, including through the use of innovative spatial analysis techniques. In particular, black/African American populations exhibit significantly poorer survival trajectories than their white counterparts for both breast and colorectal cancer survival, including both all causes and cancer-specific causes of death (OR = 1.18 to 1.55), indicating a clear need for cancer control measures focused on this population. Further, women of Hispanic/Latina ethnicity have poorer survival for breast cancer than white women for both all causes and cancer-specific mortality (OR = 1.54-1.60). Spatial analyses reveal key regions of the area that exhibit lower breast and colorectal cancer survival rates, including several regions in and around the City of Milwaukee, and several rural areas throughout southeastern Wisconsin. Cancer control efforts should consider these regions as primary targets for cancer control in southeastern Wisconsin. Information on detailed spatial patterns of cancer survival has not been previously available; thus, these findings present new opportunities for the targeting of cancer control efforts.

Limitations of this analysis include the small number of American Indian/Alaska Native individuals in the study, which may have precluded the detection of significant disparities if they do exist. The other/unknown category experienced poorer colorectal cancer survival, but an examination revealed little information regarding the individuals contained by this category, limiting interpretation. Spatial analyses are limited as they present 5-year survival rates, which do not control for covariates. Future work should develop and employ methods that adjust for important confounders, including age and stage at diagnosis.

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Emergency Department Patients' Perceptions of Radiation From Medical Imaging

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ABSTRACT

Objective: To evaluate emergency department patients' knowledge of radiation exposure and subsequent risks from computed tomography (CT) and magnetic resonance imaging (MRI) scans.

Methods: This is a cross-sectional survey study of adult, English-speaking patients from June to August 2011 at 2 emergency departments—1 academic and 1 community-based—in the upper Midwest. The survey consisted of 2 sets of 3 questions evaluating patients' knowledge of radiation exposure from medical imaging and subsequent radiation-induced malignancies and was based on a previously published survey. The question sets paralleled each other, but one pertained to CT and the other to MRI. Questions in the survey ascertained patients' understanding of (1) the relative amount of radiation exposed from CT/MRI compared with a single chest x-ray; (2) the relative amount of radiation exposed from CT/MRI compared with a nuclear power plant accident; and (3) the possibility of radiation-induced malignancies from CT/MRI. Sociodemographic data also were gathered. The primary outcome measure was the proportion of correct answers to each survey question. Multiple logistic regression then was used to examine the relationship between the percentage correct for each question and sociodemographic variables, using odds ratios with 95% confidence intervals. *P*-values less than 0.05 were considered statistically significant.

Results: There were 500 participants in this study, 315 from the academic center and 185 from the community hospital. Overall, 14.1% (95% CI, 11.0%-17.2%) of participants understood the relative radiation exposure of a CT scan compared with a chest x-ray, while 22.8% (95% CI, 18.9%-26.7%) of respondents understood the lack of ionizing radiation use with MRI. At the same time, 25.6% (95% CI, 21.8%-29.4%) believed that there was an increased risk of developing cancer from repeated abdominal CTs, while 55.6% (95% CI, 51.1%-60.1%) believed this to be true of abdominal MRI. Higher educational level and identification as a health care professional were associated with correct responses. However, even within these groups, a significant majority gave incorrect responses to all questions.

Conclusion: Patients did not demonstrate understanding of the degree of radiation exposure from CT scans and the subsequent risks associated with this exposure, namely radiation-induced malignancies. Moreover, they did not understand that MRI scans do not expose them to ionizing radiation and therefore lack this downstream effect. While patient preference is integral to patient-centered care, physicians should be aware of the significant lack of knowledge as it pertains to the selection of medical imaging tests.

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INTRODUCTION

Background

Over the past 3 decades, there has been a dramatic increase in the number of computed tomography (CT) scans ordered in the United States, increasing exposure to medical radiation nearly 6-fold.[1] The most recent national data show that 80.6 million CT scans were performed in 2012, up from 2 million scans in 1983.[1,2] Emergency departments (ED) are a significant contributor to this trend: despite only a 13% increase in overall adult ED volume, CT scanning of the cervical spine, chest, abdomen, and head for adult patients increased 463%, 226%, 72%, and 51%, respectively, in 2000-2005.[3] This was mirrored for children: a 2% increase in pediatric ED volumes was accompanied by a 435% increase in chest CTs, 366% increase in cervical spine CTs, 49% increase in abdominal CTs, and 23% increase in head CTs.[4]

While CT assists with making faster, more accurate diagnoses, physicians have become increasingly aware of the radiation exposure associated with it. This exposure carries the potential long-term risk of radiation-induced malignancies, particularly in children and young adults. Based on epidemiologic data, the radiation exposure of 1 abdominopelvic CT, which is approximately 10 mSv, confers an estimated 1:2000 risk of developing cancer.[5] Brenner and Hall estimated that approximately 2% of all cases of cancer in 2007 in the United States were caused by medical imaging,[1] while Berrington de González and colleagues suggest that this trend will continue, amounting to 29,000 cancers annually.[6]

In 2010, growing concerns over the risks of ionizing radiation from medical imaging led the Food and Drug Administration (FDA) to call for an initiative to decrease the amount of radiation attributable to medical imaging.[7] A key component of this initiative involves raising awareness of the risks medical imaging poses. However, patients' knowledge of the amount of radiation exposed to them from advanced medical imaging tests, as well as the downstream risks of that radiation exposure, has only begun to be characterized.

Importance

Recent studies suggest that patients underestimate the amount of radiation from CT compared to a chest x-ray and do not understand the potential downstream issue of radiation-induced cancers.[8,9] Despite this, patients have substantially increased confidence in their diagnostic evaluation if medical imaging, particularly CT, is performed.[9] While foundational, previous reports were limited in that they restricted patient enrollment to tertiary care centers and did not assess if patients understood the difference between sources of ionizing radiation, like CT, and imaging tests that don't subject patients to such radiation, like magnetic resonance imaging (MRI). Finally, currently published studies have not documented the relationship between patient sociodemographic characteristics and understanding of radiation exposure and subsequent risks.

Goals of This Investigation

Our primary goal was to characterize patients' knowledge of the radiation exposure associated with CT and MRI and the risk of radiation-induced malignancies. Additionally, we set out to evaluate the relationships between patient understanding of these concepts and patient sociodemographic characteristics.

METHODS

Study Design and Setting

This is a survey study of a convenience sample of ED patients conducted at 2 hospitals in the upper Midwest from June to August 2011. The coordinating center was the University of Wisconsin School of Medicine and Public Health, an academic medical center with an emergency medicine residency program and an annual ED census of approximately 45,000. The second center was Beloit Memorial Hospital, a community center with an annual ED census of approximately 35,000 that serves as a secondary training site for the university-based residency program. The study protocol was reviewed by the University of Wisconsin Health Sciences Institutional Review Board and was granted exempt status.

Selection of Participants

All adult patients (≥ 18 years) during the study period were eligible to participate; they were not required to undergo medical imaging to participate. Patients were excluded if they had altered mental status, were unable to read English, or were otherwise unable to fill out the survey. Patients were identified by ED registration personnel, who subsequently gave patients a standardized informational sheet inviting them to participate in the study. Patients were considered enrolled in the study if they submitted this voluntary survey, which lacked any identifiable information.

Methods and Measurements

The survey used in this study is based on a similar, previously published survey that had been field-tested among a small sample of ED patients prior to use on a sample of 1100 ED patients.[9] Our instrument had 2 nearly identical sets of 3 questions, one set pertaining to CT and the other pertaining to MRI (Appendix). The first question in each set gauged the patient's understanding of the relative radiation exposure of CT/MRI compared with a single chest x-ray (CXR). Using a CXR for comparison was based on multiple other studies, including the referenced survey, which universally use CXR as a baseline comparator for radiation exposure. The correct answers were based on previously reported estimates of radiation exposure associated with abdominal CT and the fact that there is no ionizing radiation exposure with MRI.[10,11] The second question assessed the patient's understanding of the relative radiation exposure of CT/MRI compared with a historical reference (Fukushima Daiichi nuclear power plant accident of 2011). This comparison was based on reports from the Japanese Atomic Industrial Forum.[12] Notably, this question was changed from the previously reported survey,[9] which used radiation exposure from the Hiroshima nuclear bomb as its comparison, due to concerns raised by the community site that the nuclear bomb reference was too emotionally charged. The final question in each set evaluated the patient's understanding of the downstream effects of radiation exposure, specifically radiation-induced malignancies.[6,11] All questions had 5 possible answer choices. Because of the change regarding the historical reference, a survey research center was consulted to review and test the modified instrument for construct validity prior to implementation.

The final portion of the survey asked for patient sociodemographic information including gender, age, race, highest level of education, household income, and whether the patient had ever worked as a health care professional. To get a sense of the generalizability of our findings, we compared the sociodemographic profile of our study population to the nationally representative sample of the American Community Survey, which uses the Census Bureau's Master Address File for its sampling frame.[13]

After being taken to a patient room, registration personnel gave patients the paper survey, which was accompanied by a standardized letter inviting patients to participate in the study. These staff were unaware of the research hypothesis and were instructed to direct patient questions regarding the survey to the treating physician. Completed surveys were handed back to ED personnel, who subsequently filed them into 1 of multiple repositories in

Table 1. Respondent Characteristics Divided by Study Site and Reported as Cumulative Data

	Study Sociodemographics			State Census Data		
	Community (N = 185)	Academic (N = 315)	Total (N = 500)	Community	Academic	State
Age in Years, Mean ± SD; Median	41±17	40±17	41±17	33.6	30.7	38.5
Health Care Professional, N (%)						
No	148 (81%)	257 (83%)	405 (83%)	N/A	N/A	N/A
Race						
White	139 (78%)	258 (84%)	397 (82%)	66%	76%	82%
Hispanic	9 (5%)	10 (3%)	19 (4%)	15%	6%	6%
Black	29 (16%)	29 (9%)	58 (12%)	10%	7%	6%
Native Hawaiian/Pacific Islander	0 (0%)	1 (0.3%)	1 (0.2%)	0%	0%	0%
American Indian/Alaska Native	1 (0.5%)	2 (0.6%)	3 (0.6%)	0.3%	0.3%	0.8%
Asian	0 (0%)	7 (2%)	7 (1%)	1%	7%	2%
Income						
< $25,000	81 (47%)	81 (28%)	162 (35%)	32%	23%	22%
$25,000 - $49,999	49 (23%)	69 (24%)	118 (26%)	33%	23%	26%
$50,000 - $74,999	21 (12%)	55 (19%)	76 (17%)	17%	19%	20%
$75,000 - $100,000	15 (9%)	34 (12%)	49 (11%)	10%	14%	14%
> $100,000	5 (3%)	50 (17%)	55 (12%)	9%	21%	19%
Gender						
Female	107 (59%)	179 (58%)	286 (59%)	53%	51%	50%
Education						
Some High School	20 (11%)	14 (5%)	34 (7%)	15%	3%	6%
High School Graduate (or GED)	84 (47%)	54 (17%)	138 (28%)	37%	16%	33.%
Some College	40 (22%)	76 (25%)	116 (24%)	20%	17%	21%
Associate's Degree	17 (9%)	29 (9%)	46 (9%)	7%	8%	9%
Bachelor's Degree	11 (6%)	82 (27%)	93 (19%)	9%	29%	17%
Graduate or Professional Degree	7 (4%)	54 (17%)	61 (12%)	5%	24%	9%

Values listed are the number of participants in each subcategory with percentages of each parent category. Age is reported as mean ± standard deviation. Data from the American Community Survey, 2008-2012 also is presented to compare this study's population with that observed in the city where each hospital was located. These data are presented as percentages, except age, which is presented as a median value. Community = data from the secondary community-based emergency department; Academic = data from the primary academic medical center; State = statewide data obtained from the American Community Survey.

each ED. Patients were informed that physicians could not answer survey questions for patients, but could answer any questions that arose after participating. Completed surveys were collected weekly from both study sites.

Survey responses were entered into Excel 2010 (Microsoft Corp, Redmond, Washington) by one of the investigators and a subset were verified by another.

Outcomes

Since our objective was to determine ED patients' knowledge of radiation exposure caused by CT and MRI, as well as their understanding of risks of radiation-induced malignancies, the primary outcome measure was the proportion of correct answers to each question on the survey. We then examined the relationship between this primary outcome measure and sociodemographic information.

Analysis

Patient sociodemographic data are presented as raw numbers and percentages. Primary outcome data are presented as percentages. We used multiple logistic regression analysis to examine the relationship between the percentage right on each question and sociodemographic variables; *P*-values of less than 0.05 were considered statistically significant. The model was built using backward and forward variable selection, utilizing all demographic variables collected in the survey. Individual missing data were omitted from analyses—we did not use imputation. Analyses were performed using Excel 2010 and SAS Analytics Pro (SAS Institute Inc, Cary, North Carolina).

RESULTS

Characteristics of Study Subjects

During the study period, a total of 315 patients at the academic hospital (of a total of 5589 patients seen) and 185 patients at the community hospital (of a total of 4988 patients seen) completed the survey. Registration personnel did not keep records of how many patients were offered participation, so we were unable to calculate a response rate. Table 1 shows sociodemographic data for survey participants, as well as data reported from the American Community Survey, 2008-2012[10] for each of the cities, as well as the state where the survey was conducted.

Main Results

Participants had a limited understanding of the relative amount of ionizing radiation from CT and MRI compared to a CXR (Table 2). Seventy-one (14.1%, 95% CI, 11.0%-17.2%) correctly indicated that CT has 100 times the amount of radiation, and 103 (22.8%, 95% CI, 18.9%-26.7%) correctly indicated that MRI has essentially no radiation compared to CXR. Similarly, 49 participants (10.1%, 95% CI, 7.5%-12.7%) expressed agreement with the true statement "patients who have 3 to 5 abdominal CTs in their lifetime have received the same radiation exposure as someone near a nuclear power plant disaster." Conversely, this statement is not true for MRI, and 304 (64.3%, 95% CI, 60.0%-68.6%) correctly expressed disagreement. Participants also had a poor understanding of the cancer risk of CT. One hundred twenty-six (25.6%, 95% CI, 21.8%-29.4%) agreed with the true statement "patients who have 3 to 5 abdominal CTs in their lifetime have an increased lifetime risk for developing cancer." However, this statement is not true for MRI, and 263 (55.6%, 95% CI, 51.1%-60.1%) correctly disagreed with this statement. The percentage of correct responses for the entire patient cohort, separated by question is displayed in the Figure.

Relationship to Sociodemographic Factors. Due to a small number of participants in some subgroups, categories for education and income level were consolidated, creating roughly equally sized groups. For education level, patients were divided into those with at least a college degree and those who had less education. For income level, subjects were divided into household incomes over $50,000 and those making less than $50,000. The following is a summary of findings:

Computed Tomography. There was a significant association between correctly answering that an abdominal CT has 100 times the radiation as a CXR and having at least a college degree ($P = 0.006$) and experience as a health care professional ($P = 0.003$). Only having at least a college degree was significantly associated with correctly answering that 3 to 5 abdominal CTs increased a patient's lifetime risk of cancer ($P = 0.004$). For all odds ratios reaching statistical significance, please see Table 3. Questions 1-3 pertain to CT.

Magnetic Resonance Imaging. Being male ($P = 0.038$), having at least a college education ($P < 0.001$), and having an annual income exceeding $50,000 ($P = 0.002$) was statistically significantly associated with correctly answering that MRI has essentially no radiation compared to CXR and that MRI scans do not increase lifetime cancer risk. Identifying as being white ($P = 0.008$), having at least a college degree ($P = 0.001$), and earning more than $50,000 annually ($P = 0.003$) was statistically related to correctly answering that MRI does not expose patients to levels of ionizing radiation similar to a nuclear power plant disaster. For all odds ratios reaching statistical significance, please see Table 3. Questions 4-6 pertain to MRI.

Table 2. Percentage of Questions Answered Correctly, Subdivided by Sociodemographic Categories

Category	Q1	Q2	Q3	Q4	Q5	Q6
Gender						
Female	15	8	28	19	64	51
Male	13	10	22	28	65	62
Race						
White	15	9	25	24	67	57
Black	9	9	33	14	49	42
Hispanic	5	21	16	16	68	68
Education						
High School	8	7	22	13	56	45
College	17	11	27	27	69	61
Income						
< $50,000	11	9	25	18	61	50
> $50,000	19	11	28	32	73	65
Health Care Professional						
No	12	9	22	22	64	56
Yes	25	11	38	27	67	54
Location						
Community	10	8	22	15	57	49
Academic	17	11	27	27	69	60
Age						
<30 years	18	8	28	19	63	52
30-60 years	13	10	25	27	67	55
>60 years	11	8	21	16	62	66

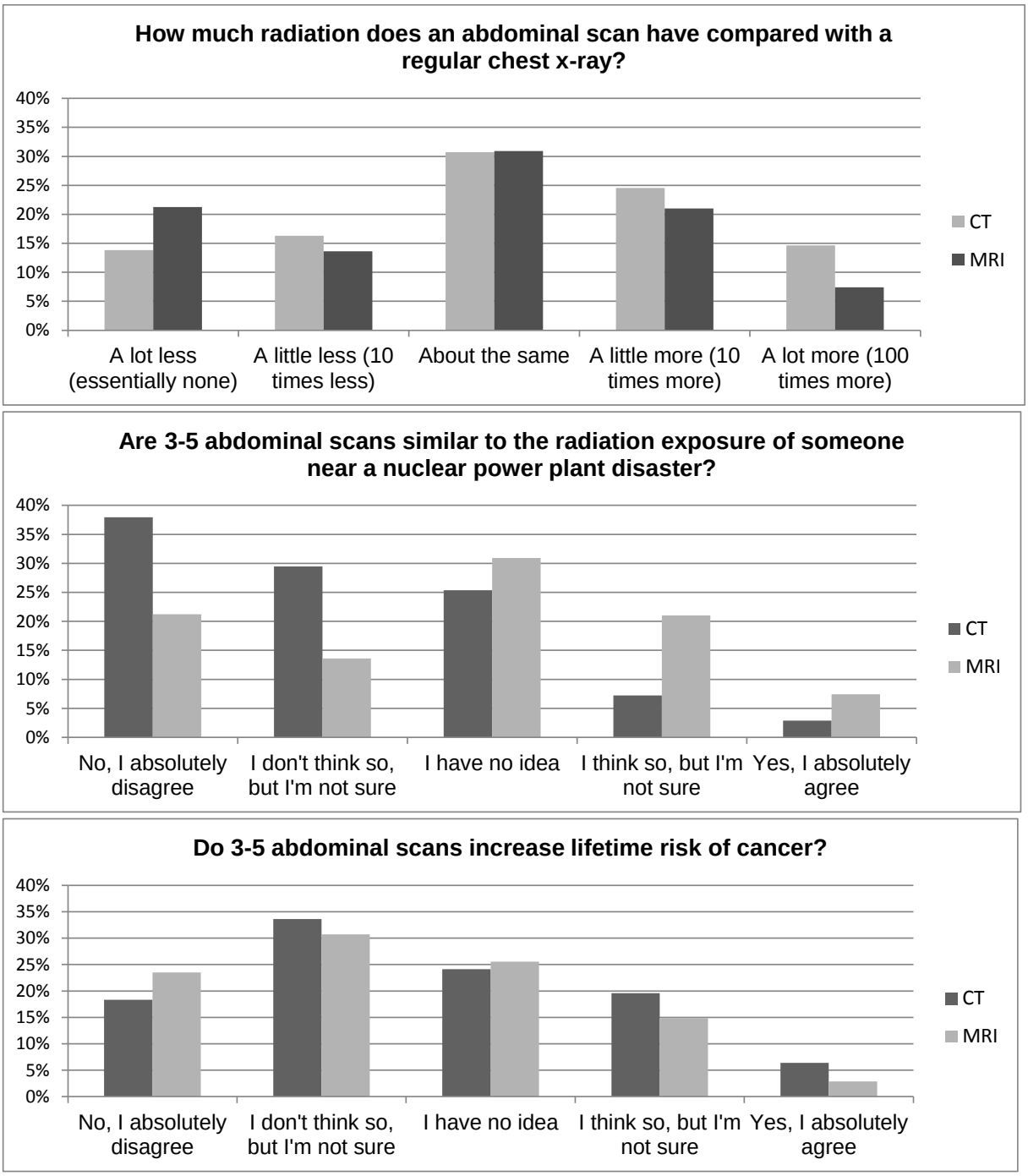
Due to having a small number of participants in some subcategories, education level, household income, and age were combined to make larger subcategories.

DISCUSSION

As reported previously,[8,9,14–16] we found that patients in the ED generally did not understand the amount of radiation associated with CT and also did not understand that this radiation exposure puts them at an increased risk of developing cancer. Our study builds upon previous findings by reporting that these same patients did not understand that MRI lacks ionizing radiation exposure and its downstream effects. Perhaps not surprisingly, we found that there was a significant relationship between answering questions correctly and having at least a college degree or experience as a health care professional. However, most patients in these categories still did not answer survey questions correctly. To date, no other study has reported patient knowledge of MRI, so we have no data to which we can compare our findings.

Few studies have delved into the field of patient preferences for medical imaging, though the funding priorities for federal agencies are now emphasizing patient-centered care and shared decision-making. We have seen that patients generally have greater confidence in their diagnostic evaluation when an imaging test is performed (particularly CT), though as we found in this study, patients don't understand the downstream radiation effects of

Figure. Distribution of Answers for Questions



Patients' answers to questions are graphed here for each question in the survey, reported as percentages, with corresponding CT/MRI questions combined. The first question in each set asked patients to estimate the amount of radiation in 1 abdominal CT/MRI compared with a chest x-ray. The second question asked patients if they believed 3 to 5 abdominal CTs/MRIs had the same radiation exposure as someone near the Fukushima Daiichi power plant disaster. The last question asked patients if they believed 3 to 5 abdominal CTs/MRIs increase someone's lifetime risk of developing cancer.

these tests.[9,15] Perhaps this lack of knowledge shouldn't be surprising since several studies have shown physicians don't have a good grasp of relative radiation exposure with CT and its downstream effects.[17–22] However, this understanding seems to be improving recently, with 95%-98% of physicians understanding that CT exposes patients to ionizing radiation[23] and 82% understanding that this radiation increases a patient's baseline risk of cancer.[24]

When Feger and colleagues sought to understand patient's preferences regarding cardiac imaging, there was general patient acceptance and comfort with use of noninvasive tests like CT

coronary angiography when compared to traditional tests like conventional angiography.[25] Moreover, there was a general preference for CT over MRI, though discussion regarding radiation effects was not part of the study. However, Hull et al showed that parents of pediatric patients' preferences for imaging were affected by a brief educational intervention regarding radiation risks of CT. Moreover, the investigators found that 93% of parents expected to have a discussion with health care providers regarding the potential benefits and harms of undergoing medical imaging.[26] Another study found that a majority of noncritical trauma patients were interested in knowing not only the risks of medical imaging, but also the costs.[27] This would make it appear that interest in shared decision making is gaining momentum and, in fact, is advocated by both emergency medicine and radiology thought leaders.[28–30] While traditionally done as a discussion, at least 1 study reports that patients were actually more interested in obtaining a handout while in the ED to review prior to undergoing CT imaging.[31]

In summary, providers should be aware that their patients do not have the knowledge base to appropriately weigh the possible harms against the possible benefits when considering whether to undergo medical imaging, particularly CT. This points to the need for better patient education as recommended by the Food and Drug Administration so that patients can make a more informed decisions regarding their health care.[7] Future directions in this field could focus on what minimum level of information would suffice for patients to truly engage in shared decision-making as it relates to choice of imaging test. As the science of medical imaging advances, particularly in the realm of ultrasound and MRI use in the ED, this will be an even more critical part of the patient encounter. Clinical decision support will be of particular value when more information and diagnostic options become available.[32]

LIMITATIONS

This is a small survey study of ED patients presenting to 2 Wisconsin hospitals over a 2-month period in 2011. Registration personnel were asked to hand out surveys to eligible participants, however less than 5% of the total ED census during the study period actually participated. There were no records kept regarding how many patients were offered participation, so we are unable to calculate a true response rate. This potentially low response rate may lead to selection bias. However, our surveyed population has similar characteristics to that reported in the American Community Survey[13] for each site (Table 1). Furthermore, patients were not monitored while taking this survey. They may have had access to online materials through smartphone-type devices, which may have artificially increased the percent of correct answers; however, few patients answered questions correctly, so we do not believe this substantially influenced the results.

Table 3. Regression Analysis Results

	Backward Selection		Forward Selection	
Question	Model Variable	Odds Ratio (95% CI)	Model Variable	Odds Ratio (95% CI)
1	College degree	2.4 (1.3,4.2)	College degree	2.4 (1.3,4.2)
	Health care provider	2.3 (1.2,4.4)	Health care provider	2.3 (1.2,4.4)
2	None		None	
3	College degree	1.7 (1,2.7)	College degree	1.7 (1.1,2.7)
4	Male	1.6 (1,2.5)	Male	1.6 (1,2.5)
	Younger age	3 (1.3,6.8)	Younger age	3 (1.3,6.8)
	College degree	1.9 (1.2,3)	College degree	1.9 (1.2,3)
5	Male	1.7 (1.2,2.8)	Male	1.7 (1,2.9)
	College degree	2.9 (1.7,4.7)	College degree	3.1 (1.9,5.2)
6	College degree	2 (1.2,3.2)	College degree	2 (1.2,3.2)

Those variables with statistically significant odds ratios are reported in this table as point estimates with 95% confidence intervals. Both backward and forward variable selection were done as part of this analysis and yielded very similar results.

Finally, we did not explicitly define what should be considered as "having health care provider experience." This may have led to information bias due to people perceiving the definition differently.

CONCLUSIONS

Patients at both academic and community EDs did not demonstrate an understanding of the radiation dose and risk associated with CT imaging. Moreover, they did not understand that MRI does not expose them to radiation and, therefore, does not impart an increased risk for developing cancer over one's lifetime. Factors associated with improved understanding were higher education and identification as a health care professional. Future directions in this line of research may focus on effective means of shared decision-making as it pertains to use of medical imaging in the diagnostic workup.

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Surveillance of Wisconsin Antibacterial Susceptibility Patterns

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ABSTRACT

Background: Antimicrobial resistance presents a threat to quality patient care. Knowledge of local antibacterial susceptibility patterns can guide clinicians in empiric antibacterial administration and assist pharmacists and infectious disease physicians in development of appropriate therapeutic pathways.

Methods: To characterize Wisconsin antibacterial susceptibility patterns and elucidate geographic or temporal variation in antibacterial resistance, a retrospective, observational analysis of antibiogram data was performed. Seventy-two members of the Wisconsin Clinical Laboratory Network (WCLN) submitted antibiograms describing clinically significant isolates tested in calendar year 2013 to the WCLN Laboratory Technical Advisory Group.

Results: In the context of commonly reported antibacterial agents, data were compiled for approximately 75,800 isolates of *Escherichia coli*; 13,300 *Klebsiella pneumoniae*; 6300 *Proteus mirabilis*; 2800 *Enterobacter cloacae*; 8400 *Pseudomonas aeruginosa*; 30,000 *S aureus*; 11,200 coagulase-negative *Staphylococcus* spp; and 13,800 *Enterococcus* spp. *P mirabilis* isolates from northern Wisconsin were more likely to demonstrate resistance than those in the southern region. In contrast, *P aeruginosa* isolates from southern Wisconsin had decreased susceptibility to a number of agents when compared to other regions. Temporal trending in decreased *E coli* and *P mirabilis* susceptibility to fluoroquinolones and trimethoprim-sulfamethoxazole was observed. Increased methicillin-resistant *Staphylococcus aureus* (MRSA) rates were observed in northwest and southeast Wisconsin. In general, northeast Wisconsin exhibited less frequency of antibacterial resistance.

Conclusions: Geographic variation exists with respect to antibacterial resistance, particularly in areas of Wisconsin adjacent to large population centers of neighboring states. Antibacterial surveillance in Wisconsin is indicated on a regular basis to assess emerging trends in antibacterial resistance. Existing WCLN infrastructure allows for such investigations.

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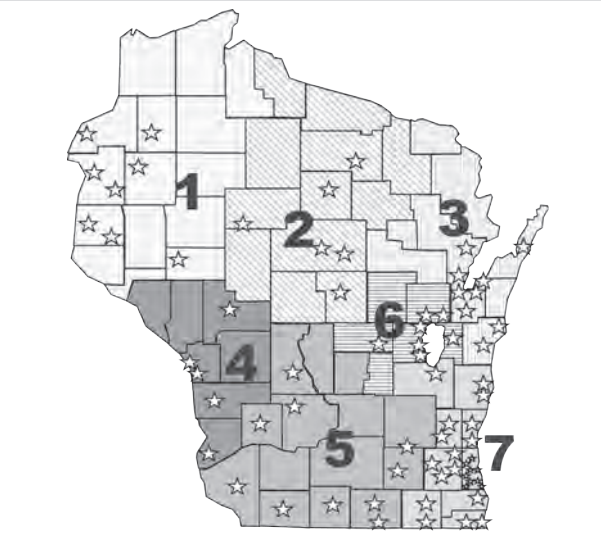
INTRODUCTION

Subsequent to the domestic terrorism events of 2001, the Wisconsin State Laboratory of Hygiene (WSLH) established a network of clinical laboratories throughout the state, known as the Wisconsin Clinical Laboratory Network (WCLN), to ensure a timely and effective response to clinical laboratory and public health needs. The WCLN is arbitrarily subdivided into 7 regions (Figure 1), with 7 clinical laboratory representatives (as well as a number of at-large clinical microbiologists) serving collectively as members of the WCLN Laboratory Technical Advisory Group (LabTAG). The mission of the WCLN has subsequently evolved into updating and training statewide colleagues on novel diagnostic options and actively participating in disease surveillance. Greater than 130 clinical laboratories, including entities without clinical microbiology services, comprise the WCLN.

Hicks et al[1] revealed that upwards of 260 million outpatient courses of antimicrobial agents were prescribed by physicians in 2011, with nearly 25% of these regimens prescribed by family practice clinicians. While the upper Midwest was not targeted as a region that could benefit from enhanced surveillance or intervention strategies with respect to overall prescription practices,[1] the high frequency of outpatient and family practice-based prescribing patterns may potentiate antimicrobial resistance in addition to that potentiated by high acuity-of-illness inpatient settings.[2] As such, surveillance of antibacterial susceptibility patterns

Figure 1. Wisconsin Clinical Laboratory Network (WCLN) Bioterrorism Preparedness Team Regions and Health Care Locations That Supplied 2013 Antibiogram Data for Antibacterial Susceptibility Surveillance



Numbers = WCLN Bioterrorism Preparedness Team Regions
Stars = Health care locations

Table 1. Regional Population Distribution and Rates of *E coli* and *S aureus* Isolate Contribution

Region	Population (2010 Census)	Reported Isolates/ 100,000 population	
		E coli	S aureus
1	565,926	1054	433
2	469,647	2655	1077
3	507,821	1641	729
4	268,520	2394	950
5	1,149,375	927	320
6	489,263	1628	611
7	2,237,110	1072	472

Shows Wisconsin Clinical Laboratory Network (WCLN) Biopreparedness Team Region population distribution and rates of *E coli* and S *aureus* isolate contribution per 100,000 population to cumulative WCLN antibacterial susceptibility surveillance.

at a statewide level, both in higher- and lower-density population settings, can be important for clinician-initiated empiric therapy, development of clinical pharmacy therapeutic recommendations, and selection of antibacterial susceptibility testing formats by the clinical microbiology laboratory. To this end, this report documents a local, data-driven antibacterial susceptibility surveillance project with the goal of generating a statewide Wisconsin antibiogram.

MATERIALS AND METHODS

Request for Antibiogram Data

During December 2014, LabTAG members extended invitations to clinical laboratories within respective Bioterrorism Preparedness Team Regions (subsequently referred to as "region") for hospital-specific antibiogram data. Tertiary and university-based clinical entities were excluded from participation, as a portion of their patient population may reside in locales outside of the respective region. Data were requested from clinically significant isolates recovered in calendar year 2013. To determine potential temporal changes in antibacterial susceptibility patterns, sites were requested to provide data, if available, from clinically significant isolates analyzed in 2009 and 2005. However, these data were excluded from analysis if the submitting entities were unable to provide 2013 antibiogram data.

Selection of Organisms for Analysis

Seventy-two entities submitted antibiograms from 2013 for consideration (Figure 1). Clinical and Laboratory Standards Institute (CLSI) states that an organism with an n value of ≥ 30 is optimal for annual antibiogram inclusion.[3] Furthermore, multiple single species isolates from the same patient are excluded from individual antibiogram inclusion. With respect to this study, a given Gram-negative bacillus meeting these criteria was reported on 6% to 100% of submitted antibiograms. *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* were reported on ≥ 50% of all submitted antibiograms and were considered for further data analysis. With the exception of *E cloacae*, the aforementioned organisms were reported on ≥ 57% of antibiograms submitted from a given region.

With respect to Gram-positive cocci, increased variation was observed in antibiogram reporting. For purposes of antibiogram generation, 63% of healthcare entities categorized *Staphylococcus aureus* as methicillin-resistant *S aureus* (MRSA) and methicillin-susceptible *S aureus* (MSSA). Therefore, all antimicrobial-specific susceptibility data for MRSA and MSSA were combined and reported as *S aureus* for the surveillance project. In analogous fashion, all permutations of non-*S aureus* species (including agents such as *S epidermidis, S saprophyticus, S lugdunensis, S warneri*, and the generic classification of coagulase-negative *Staphylococcus* spp) were combined and reported as coagulase-negative *Staphylococcus* spp. Finally, as only 50% of entities throughout Wisconsin identified enterococci to the species level, data specific to *Enterococcus faecalis, E faecium, E casseliflavus,* and *E gallinarum* were combined as *Enterococcus* spp.

Selection of Antibacterial Agents for Analysis

Thirteen antibacterials were reported on ≥ 75% of submitted Gram-negative bacilli antibiograms and were included in the final statewide compilation. Represented (sub)classes included fluoroquinolone, penicillin, β-lactam/β-lactamase inhibitor combination, cephem, aminoglycoside, nitrofuran, and folate pathway inhibitor. Within a given region, these 13 antibacterials were reported on ≥ 52% of antibiograms (data not illustrated). Two exceptions to this generalization were reporting of ceftazidime and tobramycin in region 4 (each on 40% of antibiograms). Imipenem, reported on 65% of submitted antibiograms through-

Table 2. 2013 Wisconsin Gram-negative Bacilli Antibacterial Susceptibility Surveillance

	Percentage Susceptible				
	Escherichia coli (max n 75,804)	*Klebsiella pneumoniae* (max n 13,360)	*Proteus mirabilis* (max n 6375)	*Enterobacter cloacae* (max n 2831)	*Pseudomonas aeruginosa* (max n 8493)
Gentamicin	94	99	93	99	87
Tobramycin	95	99	93	99	96
Levofloxacin	82	98	81	97	77
Ciprofloxacin	82	98	77	97	79
Ampicillin	61		83		
Ampicillin-sulbactam	68	89	91		
Piperacillin-tazobactam	97	97	99	87	93
Cefazolin	90	96	89		
Ceftriaxone	97	98	97	84	
Ceftazidime	97	98	96	86	90
Cefepime	98	98	98	98	82
Imipenem	99	99		98	87
Trimethoprim-sulfamethoxazole	81	94	83	92	
Nitrofurantoin	94	37		28	

out the state, also was included on the final compilation to sample carbapenem activity against selected Enterobacteriaceae and *P aeruginosa*.

Ten antibacterials (representing penicillin, fluoroquinolone, folate pathway inhibitor, tetracycline, macrolide, aminoglycoside, lincosamide, nitrofuran, and glycopeptide [sub]classes) were reported on ≥73% of submitted Gram-positive cocci antibiograms and included in the compilation. On a given region basis, these 10 antibacterials were reported on ≥56% of antibiograms. One exception to this generalization was reporting of gentamicin in region 2 (33% of antibiograms). Data from ampicillin, reported as a first-line agent against *Enterococcus* spp by 46% of entities, also were included on a limited basis.

Table 3. 2013 Wisconsin Gram-positive Cocci Antibacterial Susceptibility Surveillance

	Percentage Susceptible		
	Staphylococcus aureus (max n 30,982)	*coagulase-negative Staphylococcus* (max n 11,299)	*Enterococcus spp* (max n 13,893)
Penicillin	12	10	89
Ampicillin			93
Methicillin	62	49	
Levofloxacin	65	60	66
Gentamicin	98	90	
Erythromycin	47	39	
Clindamycin	72	63	
Nitrofurantoin	99	99	93
Trimethoprim-sulfamethoxazole	98	66	
Tetracycline	94	85	
Vancomycin	99	99	93

Analysis

Mean percentage susceptibility data were calculated for given organism/antibacterial combinations solely on the basis of all percentage susceptible data submitted from a region, irrespective of n values. The significance test of proportions determined whether region-specific variances in Gram-negative bacilli and Gram-positive cocci antibacterial surveillance from 2009 to 2013 were significant. The alpha level was set at 0.05 before the investigations commenced and all *P* values are 2-tailed.

RESULTS

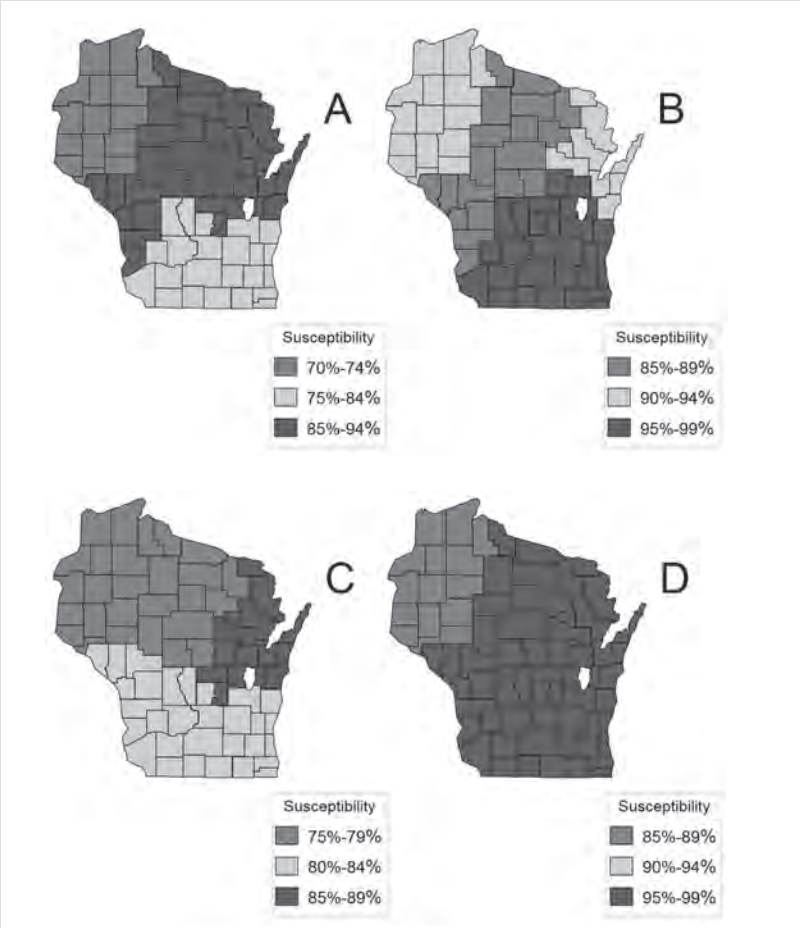
Representation Across Regions

To assess bias potential toward large population regions, frequency of *E coli* and *S aureus* antibiogram reporting per 100,000 population was calculated for each region on the basis of 2010 US Census data. Five of 7 regions contributed 927 to 1641 reports of *E coli*-specific data per 100,000 population, including region 7 (Table 1). Regions 2 and 4 contributed 2655 and 2394 *E coli* isolates per 100,000 population, respectively, to this project. In similar fashion, 320 to 729 isolates of *S aureus* per 100,000 population were submitted from 5 of 7 regions. Regions 2 and 4 submitted data from 1077 and 950 *S aureus* isolates per 100,000 population, respectively.

Wisconsin Gram-negative Bacilli Antibacterial Surveillance, 2013

Susceptibility data from 75,804 isolates of *E coli* were compiled (Table 2). Noteworthy findings included susceptibility rates of 61% to ampicillin, 68% to ampicillin-sulbactam, and 94% to nitrofurantoin. Susceptibility rates compiled from 13,360 *K pneumoniae* revealed increased susceptibility rates to fluoroquinolone agents (levofloxacin, ciprofloxacin) and trimethoprim-sulfamethoxazole when compared to commonly encountered enteric Gram-negative bacilli such as *E coli* and *P mirabilis*. *In vitro* activity of ampicillin and ampicillin-sulbactam against 6375 isolates of

Figure 2. Geographic Variation in *P mirabilis* Susceptibility to Ampicillin (A), Tobramycin (B), Trimethoprim-Sulfamethoxazole (C), and Third- and Fourth-Generation Cephems (D), Wisconsin 2013



P mirabilis was increased over that observed in *E coli*. Analysis of 2831 isolates of *E cloacae* revealed increased rates of cefepime susceptibility when compared to ceftriaxone and ceftazidime. On a statewide basis, piperacillin-tazobactam and tobramycin exhibited best *in vitro* activity against a compilation of 8493 *P aeruginosa* isolates. Susceptibility rates to fluoroquinolone agents were generally lower than aminoglycosides (gentamicin, tobramycin).

Wisconsin Gram-positive Cocci Antibacterial Surveillance, 2013

Susceptibility data from 30,982 isolates of *S aureus* revealed a statewide MRSA rate of 38% (Table 3). Data also revealed high rates of *S aureus* susceptibility to trimethoprim-sulfamethoxazole and tetracycline, as well as a 99% susceptibility rate to nitrofurantoin in a subset of 18,467 isolates. Decreased *S aureus* susceptibility to levofloxacin (65%), erythromycin (47%), and clindamycin (72%) also was noted. In contrast to *S aureus*, 11,299 isolates of coagulase-negative *Staphylococcus* spp demonstrated less *in vitro* activity against trimethoprim-sulfamethoxazole and tetracycline. Statewide resistance of 13,893 isolates of *Enterococcus* spp to vancomycin was 7% in 2013 (Table 3). Susceptibility rates of subsets of 8456 isolates to penicillin and 8678 isolates to ampicillin were 89% and 93%, respectively.

Regional Differences in Antibacterial Susceptibility Profiles

A dichotomy of geographic resistance patterns was noted for *P mirabilis* and *P aeruginosa*. Decreased rates of *P mirabilis* susceptibility to ampicillin (Figure 2A), tobramycin (Figure 2B), trimethoprim-sulfamethoxazole (Figure 2C), and third-/fourth-generation cephems (Figure 2D) were observed particularly in regions 1 and/or 2. Analogous susceptibility rates were generally higher in regions 5-7, as well as region 3. In contrast, decreased susceptibility of *P aeruginosa* to piperacillin-tazobactam (Figure 3A), ceftazidime/cefepime (Figure 3B), gentamicin (Figure 3C), and ciprofloxacin (Figure 3D) was particularly noted in region 7 and, in some instances, observed in regions 3, 5, and/or 6. Northern regions of the state exhibited increased susceptibility of *P aeruginosa* to these agents.

Finally, distribution of clinically significant MRSA mirrored pockets of increased resistance in Wisconsin. Regions 1 and 7 exhibited MRSA rates of 44% and 40%, respectively, in 2013. Other regions demonstrated reduced rates, including region 3 with a rate of 27% (Figure 4A). Similarly, a significant focus of vancomycin-resistant *Enterococcus* spp was observed within region 7 (Figure 4B).

Temporal Differences in Antibacterial Susceptibility Profiles

Fifty-six of the 72 clinical entities supplying antibiogram data for 2013 provided analogous data from 2009. When comparing Gram-negative bacilli and Gram-positive cocci surveillance compilations from the 2 years at the regional level, variances of ≥5% were observed for 14.9% and 29.7% of organism/antibacterial combinations, respectively ($P < 0.0002$; Table 4).

The vast majority of instances of reduced susceptibility in 2013 profiling was observed with Gram-negative bacilli ($P < 0.0002$ versus reduced susceptibility in Gram-positive cocci). Nineteen of the 43 instances of decreased Gram-negative bacillus susceptibility were noted in *P mirabilis*. Evidence existed for the emergence of *P mirabilis* with reduced susceptibility to ciprofloxacin in regions 1 and 3 in 2013 when compared to 2009 (Table 5). A second temporal paradigm of interest is *E coli* suscepti-

bility to levofloxacin. While regions other than region 3 experienced a reduction in susceptibility from 2009 to 2013, modest improvement actually was documented in region 7.

In contrast to Gram-negative bacilli antimicrobial surveillance of 2009-2013, substantial variances in 2013 Gram-positive cocci surveillance were characterized by increased susceptibility (Table 4). Thirty-four of 40 such improvements were noted in staphylococci. In 2009, the MRSA rate reported from clinically significant isolates in region 2 was 35%. This rate ranged from 40% to 49% in the other six regions. By 2013, region 2 reported an MRSA rate of 38%, while analogous rates in four other regions demonstrated improvement, including a decline from 40% to 27% in region 3. In addition, region 7 experienced a decrease in MRSA rate from 49% to 40% (Table 5).

DISCUSSION

Limitations exist with respect to this format of surveillance. It must be assumed that laboratories are utilizing either commercial antibacterial susceptibility testing formats cleared by the Food and Drug Administration (processed per package insert guidelines) or assays that have undergone rigorous laboratory self-verification. Furthermore, it must be assumed that laboratories are assessing clinically significant isolates[4] using guidance provided by agencies such as CLSI[5-7] or the European Committee on Antimicrobial Susceptibility Testing (www.eucast.org). Moreover, on the basis of factors such as local clinician antimicrobial preference, pharmacy purchasing agreements, and commercial susceptibility testing vendor panel formats, a number of antibacterials were not common to all submitted antibiograms. In response, we used a majority approach for a given antibacterial to be considered for compilation. As a result, fewer antibacterials were included in the final compilation.

The antibiogram approach to monitor-

Figure 3. Geographic Variation in *P aeruginosa* Susceptibility to Piperacillin-Tazobactam (A), Anti-pseudomonad Cephems (B), Gentamicin (C), and Ciprofloxacin (D), Wisconsin 2013

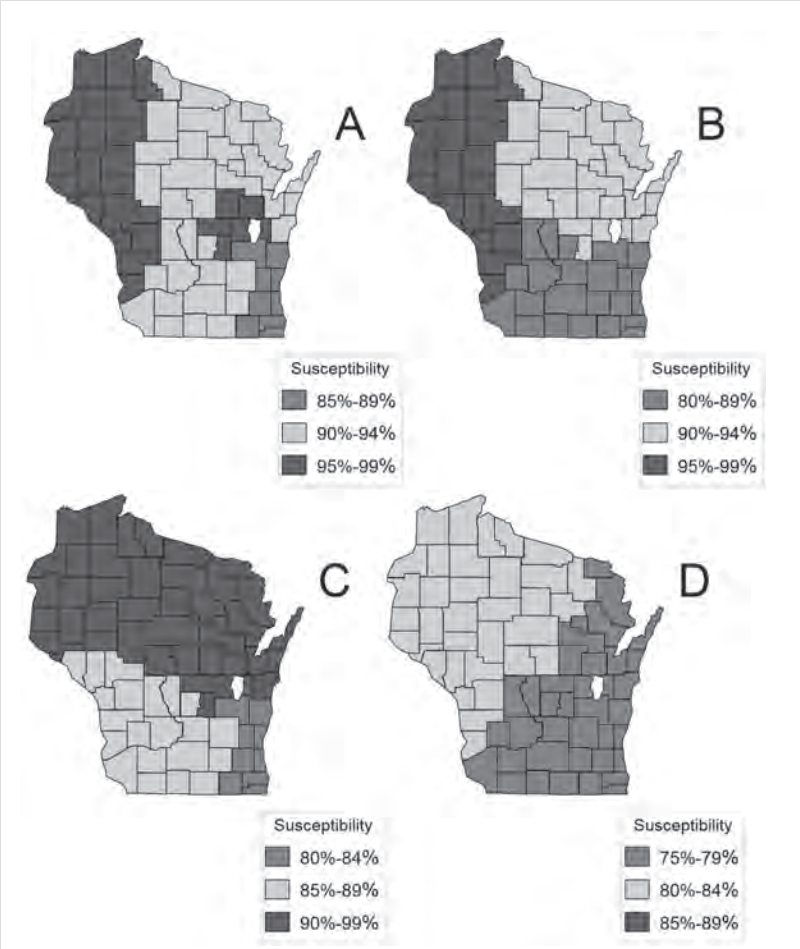


Figure 4. Geographic Variation in Distribution of Methicillin-Resistant *Staphylococcus aureus* (A) and Vancomycin-Resistant *Enterococcus* spp (B) Isolates, Wisconsin 2013

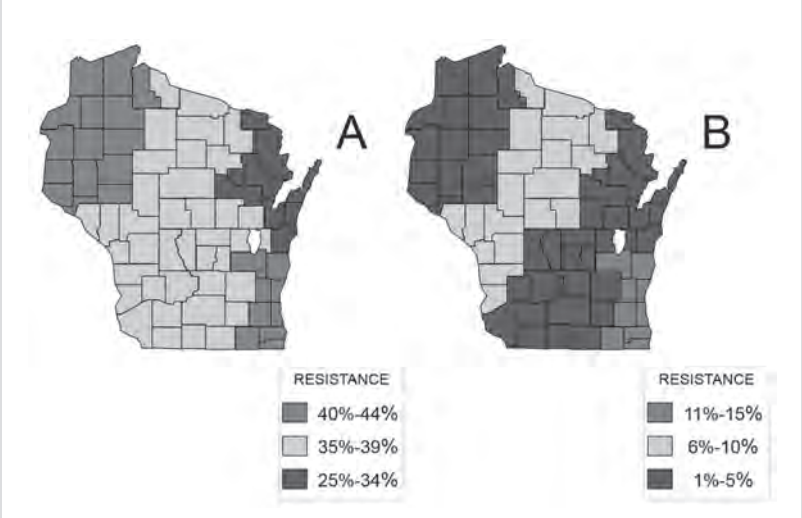


Table 4. Summary of Significant, Region-specific Variances in Gram-negative Bacilli and Gram-positive Cocci Antibacterial Susceptibility Surveillance, Wisconsin 2009-2013

Antibacterial Surveillance	Number of Organism/ Antibacterial Observations	Number of Variances[a] ≥ 5%	Number of Variances ≥ 5%	
			Reflective of Increased Susceptibility	Reflective of Decreased Susceptibility
Gram-negative bacilli	382	57 (14.9)[b]	14 (24.6)[c]	43 (75.4)[c]
Gram-positive cocci	175	52 (29.7)[b]	40 (76.9)[c]	12 (23.1)[c]

[a] Data from year 2009 used as a baseline in determination of variance.
[b] Value in parentheses represents percentage of organism/antibacterial observations.
[c] Value in parentheses represents percentage of variances ≥ 5%.

Table 5. Selected Instances of Region-Specific Temporal Changes in *E coli, P mirabilis*, and *S aureus* Antibacterial Susceptibility, Wisconsin 2005-2013

Organism	Antimicrobial	Location	Percentage Susceptible by Year 2005	2009	2013
E coli	levofloxacin	Region 1	91	80	81
		Region 3	92	85	86
		Region 7	85	78	81
		Wisconsin	90	83	82
P mirabilis	ciprofloxacin	Region 1	89	79	66
		Region 3	91	90	82
		Region 7	84	76	77
		Wisconsin	88	82	77
	trimethoprim-sulfamethoxazole	Region 1	84	84	77
		Region 3	95	91	86
		Region 7	88	82	83
		Wisconsin	89	84	83
S aureus	methicillin	Region 1	71	55	56
		Region 3	55	60	73
		Region 7	48	51	60
		Wisconsin	57	56	62

ing emerging resistance may be impacted by additional factors. The end point of the antibiogram, percentage susceptibility, does not specifically relate frank resistance or increases in rates of intermediate resistance. In certain cases, monitoring of changing minimum inhibitory concentrations for a given organism/antimicrobial combination can detect local increases in the rate of resistance before such changes can be observed in an antibiogram.[8] Antibiograms also have an inability to track emergence of resistance during a course of therapy.[9] In addition, antibacterial susceptibility testing practices can impact final antibiogram data by way of selective reporting.[10]

Another mitigating factor relates to preparation of the document itself. Individual antibiograms may be subject to deficiencies such as inclusion of duplicate isolates, reporting of misleading organism/antimicrobial combinations, insufficient n values, lack of yearly updating, and reporting of inappropriate data, such as organisms that are inherently resistant to a given antibacterial.[11-13] As one example in our 2013 compilation, the susceptibility rate of Wisconsin *S aureus* isolates to vancomycin was 99%. Due to the nature of the surveillance, we were unable to confirm true vancomycin resistance or intermediate susceptibility within this ~1% of staphylococci. A preliminary finding of vancomycin-resistant *S aureus* requires infection control notification and referral of the isolate to a public health laboratory for confirmation.[5]

To circumvent one issue relative to antibiograms from smaller facilities, only organisms with an n ≥ 30 were included in compilations. Unfortunately, as a result of this practice, data from several significant pathogens were excluded. In 2013, *Streptococcus pneumoniae* data were reported on only 32 antibiograms (44% of submitted antibiograms). Statewide *S pneumoniae* susceptibility to penicillin was 71% from 1228 isolates—largely unchanged from the 72% value reported from 1242 isolates (28 antibiograms) in 2009 (data not illustrated). *S pneumoniae* susceptibility to levofloxacin in 2013 (27 antibiograms; 840 isolates) was 98% and largely unchanged from the 99% value derived in 2009 from limited assessment of 826 isolates. With respect to chemoprophylaxis of penicillin-allergic pregnant females for beta-hemolytic *Streptococcus* group B colonization,[14] CLSI standards specify performance of both erythromycin and clindamycin susceptibility testing (with inclusion of inducible clindamycin resistance assessment), but routine reporting of only clindamycin data.[5-7] In 2013, only 21 submitted antibiograms (29% of all antibiograms) reported *Streptococcus agalactiae* susceptibility to clindamycin. The limited dataset (1801 isolates) revealed a 42% susceptibility rate—a decrease from the 71% value compiled from 15 antibiograms submitted from 2009 (868 isolates). Clearly this is an organism/antibacterial combination that requires future surveillance.

As a result of such limitations, use of the term "state antibiogram" to describe the end product of this project is not justified; "antibacterial surveillance" is more appropriate. One could further posit that the best means of performing statewide antimicrobial surveillance would be akin to surveillance programs such as CAPITAL, SENTRY, and SMART,[15-17] by which a centralized testing laboratory uses a standardized means of testing isolates sent from a number of geographic locales. Conversely, Halstead

et al[18] illustrated the value of a metropolitan antibiogram that was a compilation of 10 local antibiograms. In one instance, a 13% difference in rate of *S pneumoniae* susceptibility to penicillin was noted in the compilation when compared to a multistate summary. Moreover, Fridkin et al[19] stated that hospital antibiograms also were reflective of susceptibility patterns associated with health care-acquired infections.

Multiple health care entities within each region participated in this project. This removed bias inherent to large entities within a region and resulted in random distribution of sites within regions (Figure 1). One exception to this concept was the lack of sites (including nontertiary care facilities) within Dane County of region 5. When contemplating this uneven distribution, one must remember that participation was voluntary. Furthermore, university-based and tertiary care facilities were excluded from analysis because the study design sought to assess resistance rates as a function of geography. It was inferred that patients residing in multiple and perhaps distant regions comprised a substantial proportion of patient population at tertiary care facilities. The voluntary nature of participation in this project may provide explanation for the potential overrepresentation of less populous regions 2 and 4 in this surveillance project (Table 1).

An example of where benefits of antimicrobial stewardship programs may already be evident in some areas of Wisconsin is with respect to levofloxacin and *E coli* (Table 5). While a number of regions saw a reduction in susceptibility with this combination from 2009 to 2013, the region 7 susceptibility rate improved. When this paradigm was extended to a limited focal surveillance involving 48 antibiograms in 2005 (42,551 isolates), one can observe a trend of increasing *E coli* resistance to levofloxacin statewide and in regions 1 and 3 (Table 5). However, the trend of decreased susceptibility appears to have stabilized in region 7. Limited surveillance of *P mirabilis* beginning in 2005 (4424 isolates statewide) uncovered a secondary wave of resistance. Susceptibility rates to ciprofloxacin and trimethoprim-sulfamethoxazole decreased statewide and in regions 1 and 3 between 2005 and 2013, while region 7 susceptibility rates stabilized between 2009 and 2013. Finally, the 2005 statewide MRSA rate for 21,865 isolates was 43%. While this value decreased over the following 8 years statewide, including regions 3 and 7 (Table 5) an MRSA rate increase was experienced in region 1.

CONCLUSION

Despite limitations to antibiogram development and construction, statewide antibiogram compilation provides both an acceptable glimpse of antibacterial susceptibility patterns and a baseline for temporal comparisons. Our current investigation implicates *E coli*, *P mirabilis*, MRSA, fluoroquinolone agents, and trimethoprim-sulfamethoxazole as major factors in geographic and temporal variation of antibacterial susceptibility throughout Wisconsin. Complete datasets from the 2009 and 2013 components of this statewide antibacterial surveillance project are posted to the WSLH web portal: www.slh.wisc.edu/wcln-surveillance/wcln/wcln-resources/. In the future, the WCLN possesses sufficient infrastructure to allow for additional surveillance efforts to monitor changes in resistance patterns or to justify regional antimicrobial stewardship efforts.

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Barriers to Compliance in a Home-Based Anterior Cruciate Ligament Injury Prevention Program in Female High School Athletes

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ABSTRACT

Importance: Supervised injury prevention programs can decrease injuries in female high school athletes. Research regarding home-based injury prevention programs is limited.

Objective: To identify barriers to compliance with a home-based injury prevention program in rural Wisconsin female high school basketball players.

Design: Cross-sectional study including participants from 9 rural Wisconsin high schools. Participants were instructed in appropriate exercise form and DVD use in a group-based format. Participants were instructed to perform the home-based program 3 times per week for 8 weeks. Participants then completed a survey regarding their program compliance.

Setting: Exercise instruction and surveys were completed in the participant's high school gymnasium.

Participants: Female students in grades 9-12, who intended to play basketball, were invited to participate. Of the 175 eligible students, 66 enrolled in the study.

Intervention: The intervention consisted of a DVD-based injury prevention program.

Main Outcome: Our hypothesis—that compliance with a home-based injury prevention program would be low—was established prior to study commencement. Outcome measures consisted of self-reported responses by participants. Statistics are descriptive.

Results: Follow-up surveys were completed by 27 of 66 participants, with 50% reporting performing the injury prevention program 0-3 times per week. The reasons for low compliance included "I did not have time to do the program," followed by "I forgot to do the program."

Conclusions and Relevance: Wisconsin female high school basketball players demonstrated very low compliance with a home-based injury prevention program. This paper identifies barriers to compliance.

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INTRODUCTION

Sports-related lower extremity musculoskeletal injuries are common in females; 52% of female high school athletes in Wisconsin reported sustaining a sports-related injury that required them to modify or miss participation.[1] Among directly comparable high school sports (soccer, basketball, and baseball/softball), girls sustain more severe injuries than boys.[1] In the short term, this may result in less overall sport participation for females; the long-term consequences may include chronic pain, decreased function, and a decrease in lifetime physical activity.[2]

As compared to males, females are up to 8 times more likely to sustain a non-contact tear of the anterior cruciate ligament (ACL) in the knee.[3] These injuries often require surgery, lengthy rehabilitation, and result in an increased risk of degenerative arthritis.[3] However, recent studies have reported that utilization of a preseason and in-season injury prevention program can decrease the rate of ACL tears in females.[4] A program consisting of strengthening, jumping drills, and agility drills was effective in decreasing the incidence of ACL tears in high school female soccer players by 88%.[5] Other studies have reported similar findings.[4]

As with other injury prevention programs, these effective programs were supervised;[4,6,7] athletes who were highly compliant had a lower rate of ACL tears compared to participants with poor compliance.[8,9] However, few studies to date have used a home-based injury prevention program.[10] Because of differences in program design, lack of a control group, and a lack of tracking injury data,[10] it cannot be determined if a home-based program is effective in preventing ACL tears.

Table 1. Exercise Components and Progression of Home-Based, 8-Week Injury Prevention Program

Weeks 1-3		
	Number of Exercises/ Category[a]	**General Exercise Concepts**
Strength	5	Most exercises were double limb support, such as squats, stationary lunges, and bilateral heel raises. Most exercises focused on the sagittal plane.
Plyometric exercise	2	Jumps were 2-footed; most movement was in the sagittal plane, with small movements in the frontal plane.
Balance	2	Balance activities were single leg, primarily on the ground with small self-perturbations with the other lower extremity (or the upper extremity, like dribbling a basketball).
Weeks 4-6		
	Number of Exercises/ Category[a]	**General Exercise Concepts**
Strength	4	Strength exercises progressed to single leg (alternating lunges), and incorporated frontal (side raises standing on a labile surface[b]) and transverse plane movements (diagonal lunges).
Plyometric exercise	3	Jumps progressed to "take off 2, land 1" and jumping was performed in the frontal and transverse planes.
Balance	2	Single leg activities were performed on a labile surface,[b] while concurrently performing perturbation with the opposite lower extremity or the upper extremity.
Weeks 7-8		
	Number of Exercises/ Category[a]	**General Exercise Concepts**
Strength	3	Exercises were primarily in the frontal and transverse planes and involved stepping onto a labile surface,[b] oftentimes with upper body rotation.
Plyometric exercise	4	All jumps were single-footed and focused primarily on the frontal and transverse planes.
Balance	2	Balance exercises were dynamic (such as a single leg squat), and were performed on a labile surface,[b] and sometimes required the athlete to close her eyes to minimize visual input.

[a] Although each exercise had more than one component (a strength and balance component, for example), the exercise was categorized according to the primary focus of the exercise.
[b] Thera-Band Stability Trainer

To date, an at-home, DVD-based injury prevention program to decrease knee injuries in female high school basketball players has not been performed. Although barriers to compliance with home-based exercises after ACL reconstruction have been identified, these factors—increased stress and negative mood[11]—relate directly to surgical reconstruction. It is unknown what barriers may be associated with a home-based knee injury prevention program. Therefore, the purpose of this study was to identify barriers associated with performing an at-home, DVD-based, lower extremity injury prevention program to reduce knee injuries in rural high school female athletes.

METHODS

Subjects

During the 2012-2013 school year, 9 high schools in Wisconsin were selected by convenience for study participation. Schools that contracted athletic training services from a local hospital that was a voting member of the Rural Wisconsin Health Cooperative (RWHC) were invited to participate. The high school was considered rural because the local hospital was a member of the RWHC. Within the 9 selected sschools, enrollment averaged 75 students per class. Females who had played basketball the previous year and all incoming freshman females were contacted and invited to participate. Females were excluded if they sustained a lower extremity surgery within the past year, had spinal surgery within the past 6 months, had an orthopedic condition that precluded them from exercising, or if they had utilized a formal rehabilitation program for a lower extremity orthopedic injury in the past 3 months. Of the 255 female athletes who were contacted, 175 planned to participate in basketball and were eligible for the study. Sixty-six individuals chose to participate in the study, which was approved by the Institutional Review Board at the University of Wisconsin-Madison.

DVD Exercise Program Content

The 8-week injury prevention program was designed by the authors, based upon existing, successful supervised injury prevention programs.[5] The DVD-based program was designed to progress the female athlete's strength, balance, and jumping and landing technique with minimal risk of injury. Each training session was approximately 15 minutes in length and was comprised of 3 components: strength training, plyometrics, and balance. The exercises progressed from Level 1(weeks 1-3), to Level 2 (weeks 4-6) to Level 3 (weeks 7-8) (Table 1). The DVD demonstrated both improper and proper exercise form and provided repetitions and sets of each exercise; the participant simply had to complete the exercise at the same rate as the age-appropriate model on the DVD. For each Level, there were three different exercise programs from which the athlete could choose for a total of 9 programs. This was done to encourage variety and minimize boredom. Lastly, a section was created that reviewed exercise form; the participant was encouraged to refer back to this section when necessary.

Exercise Program Instruction and Data Analysis

Once written parental consent and written subject assent was obtained, participants met with one of the authors (JTN) in a

group-based format at their local high school gymnasium. This meeting occurred 8 to 9 weeks prior to the onset of basketball season, in late August, for all 9 schools. At this meeting, participants were instructed in DVD use, provided necessary equipment (DVD, Thera-Band, and Thera-Band Stability Trainer) and instructed in use of the exercise log. The exercise sessions were led by an author (JTN) and the licensed athletic trainer from the respective school. Upon successful completion of the training session, which included return demonstration of the exercises, participants were instructed to perform the exercises at home 3x/week for the next 8 weeks. The participants were not contacted during the 8-week time period. Upon completion of the 8-week program, participants turned in their exercise log and equipment. They also completed a survey developed by the authors that questioned the participant's compliance, likes, and dislikes of the home-based program. Although local coaches were aware of the program, they had no knowledge of who was participating in the study. In addition, although the licensed athletic trainers were aware of which athletes were study participants and possibly saw the athletes at school as a fall sport participant, they did not offer encouragement or discuss the study with the athlete.

Descriptive statistics were used to characterize the sample. Frequencies were used to summarize participants' responses regarding grade, fall sports participation, completion of post-training surveys, frequency with which they performed the program, reasons for noncompliance, and user satisfaction and feedback from those who were compliant with the program.

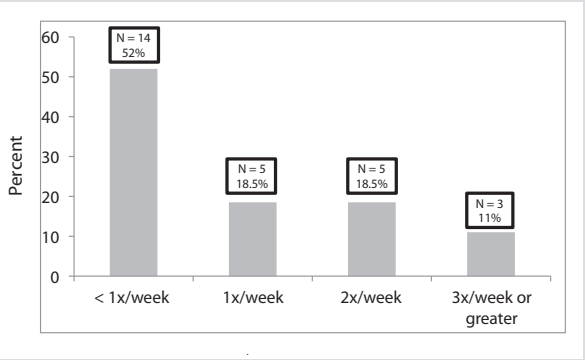
RESULTS

Of the 175 high school females who participated in basketball during the 2012-2013 season, 66 participated in the initial training session for a 38% participation rate. Eight weeks later, 27 of the 66 females (41%) present at the initial training session completed the compliance survey and provided feedback regarding the home-based injury prevention program.

Of the 66 females who participated in the initial training session, the majority (40.90%) were in grade 9; the least were in grade 12 (13.64%). Likewise, the majority of participants who completed post-training compliance survey were also in grade 9 (48.15%), whereas only 7.41% of those in grade 12 completed the post-training surveys. Approximately 80% of the 66 females also participated in a fall sport, either volleyball (71.21%) or cross country (10.60%). Of those who completed the post-training surveys (n = 27), 21 (77.8%) participated in volleyball, while 1 (3.7%) participated in cross country. Five (18.5%) of those who completed the post-training surveys did not participate in a fall sport.

The females who completed the post-training survey (n = 27) were asked to report the frequency that they performed the program during weeks 1-4, as well as during weeks 5-8. The average

Figure. Frequency (%) Which Participants Reported Performing the Exercise Program for the 8-Week Period[a]



[a] The goal was to perform the exercises 3 times per week.

Table 2. Self-Reported Reasons for Lack of Completion of the Injury Prevention Program[a]

Statement	N (%)
I did not have time to complete the program at home.	21 (78)
I forgot to do the program.	12 (44)
I lost my equipment.	1 (4)
The program made me too sore in my muscles.	0 (0)
I didn't have space in my house to do the program.	0 (0)
I did not like the program.	0 (0)
I did not have home media equipment to do the program.	0 (0)

[a] Because participants could select more than 1 option, the percentage is >100%.

frequency with which they completed the program is outlined in the Figure. The majority (52%) reported performing the program < 1x/week during the 8-week period. When weeks 1-4 were compared to weeks 5-8, the frequency of participation was similar. In other words, there was not a significant increase or decrease in participation over the 8-week period. No attempt was made to contact the girls who did not complete the post-test survey (n = 39).

When asked why they did not complete the program as requested, 78% of the participants reported they "did not have time to complete the program," and 44% reported they "forgot to do the program." No participants reported that they were too sore in their muscles, had a lack of space in their home, or that they did not like the program as a reason for a lack of compliance (Table 2).

Of the 27 participants who completed post-training surveys, 7 (26%) completed the program, > 11 times (out of 24 total sessions), or at least 50% of the requested time. Six of these 7 participants thought that doing the program made their legs stronger, made their balance better, and would make them a better basketball player and thus would do the program again. Of the 20 participants (74%) who reported doing the program less than 50% of the time, most felt the DVD was easy to use and the exer-

Table 3. Feedback From Participants Who Completed the Program <50% of the Time Compared to Those Who Completed the Program >50% of the Time

Statement	Mean Likert Score[a]	
	< 50% (n = 20)	> 50% (n = 7)
The DVD was easy to use.	4.41	4.71
Exercises were easy to follow.	4.39	4.57
The exercise program was too long.	3.11	2.43
The exercise program was too short.	2.44	2.57
I got bored doing the exercises.	3.53	3.29
The equipment (bands, balance trainers) was easy to use.	3.94	4.57
I liked the music on the DVD.	3.39	1.43
I listened to my own music most of the time.	2.82	3.29
I think doing this program made my legs stronger.	3.53	4.43
I think doing this program made me jump better.	3.44	3.86
I think doing this program made my balance better.	3.56	4.14
I think I will be a better basketball player because I did this program.	3.50	3.86
If I had the chance, I would do this program again before basketball season.	3.47	3.57

[a] Likert scale: 5= strongly agree, 4 = agree, 3 = neutral, 2 = disagree, 1 = strongly disagree.

cises were easy to follow (Table 3). The group with low compliance also reported average lower Likert scores related to improved leg strength, improved balance, and improved jumping skills as compared to the group with higher compliance (Table 3).

DISCUSSION

This study identifies barriers to performing a home-based exercise program for lower extremity injury prevention in female high school basketball players in rural Wisconsin. The most commonly identified barriers included (1) a lack of time and (2) forgetting to do the program. None of the athletes identified muscle soreness, a lack of space, or a lack of home media equipment as a barrier to compliance.

The most common self-reported barrier to program compliance was a lack of time. In our present study, over 80% of the participants reported competing in a fall sport. Because of the demands of the fall sport, in addition to other extracurricular activities and homework, the participants may have been limited on time available to complete the program at the requested frequency. In addition, children from rural families devote 1 to 2 hours/day to farm work.[12] All of these factors may have contributed to the participants' reported lack of time to complete the program.

Another reason for lack of compliance was that the participants simply forgot to perform the program. We purposely chose not to provide participants with reminders because we wanted to determine how compliant girls would be without any external reminders. Although asking parents to provide regular reminders to improve compliance is likely not realistic, the coach of the sport in which the female is participating may be able to offer reminders at practice.

Other studies have reported low compliance with home-based exercise programs in the high school population.[13] Even with face-to-face reminders, compliance with home programs has been reported to be as low as 40%. In the present study, we did not communicate with the athletes to encourage compliance. As our findings are similar to this study,[13] providing face-to-face communication alone may not improve compliance.

In contrast, compliance with a 6-week home-based wobble board training program was investigated. Participants received biweekly in-person assessments and progressions in addition to weekly telephone calls.[14] It appears that face-to-face interaction in combination with weekly reminders from a health care professional may be effective in increasing compliance. Unfortunately, in the real world setting outside of a structured research protocol, there may be limited contact with a researcher who can provide exercise reminders.[15] However, utilization of a health care professional who has daily contact with the athlete, such as a high school athlete trainer, may be able to provide reminders, leading to increased compliance.

Dissemination and implementation of effective injury prevention programs and subsequent compliance with these programs is essential to reducing the burden of sport-related injuries. A meta-analysis reported that higher compliance rates with prevention programs was associated with lower rates of ACL injury incidence.[9] Other studies have demonstrated similar findings.[16] As such, identifying barriers to implementation and compliance and creating strategies to overcome these barriers is paramount. Low levels of conflict, high levels of cohesion and organization, and good communication patterns have been associated with better regimen adherence.[17] As such, high school athletic trainers, who interact frequently with the athletes and coaching staffs, are ideal candidates to take a leadership role in this area. Athletic trainers are uniquely positioned to implement and supervise adherence to these ACL injury prevention programs.

Wisconsin basketball coaches surveyed about their use of injury prevention programs reported a lack of expertise as one reason for not implementing them.[18] Coaches also cite lack of time and space as barriers to perform injury prevention programs. Athletic trainers should be encouraged to take a more prominent role in advising coaching staffs how prevention programs can be implemented in a short, efficient manner requiring minimal equipment and space. In a study by LaBella et al,[19] coaches were instructed in how to lead a 20-minute neuromuscular warm-

up that was aimed at reducing lower extremity injuries in high school female athletes. Compared to a control group, the coach-led warm-up group of female athletes had less noncontact lower extremity injuries as compared to the control group.[19]

Studies have shown that enhancing long-term adherence requires individualization and should take into account the patient's age, lifestyle, motivation, interest, and usual methods of enforcement.[20] This requires that the interventions must be tailored to an individual's needs to succeed. In our study, we designed an injury prevention program specifically for female high school basketball players: The background of the DVD was basketball-based and the drills utilized a basketball and/or basketball-specific drills whenever possible. At each level, there were 3 different individual programs; as such, we felt we provided the participant with a variety of exercises routines from which to choose. In addition, the models in the video were young females of average height and weight. Feedback from the most compliant participants was overwhelmingly positive; dislike of or difficulty using the DVD or performing the exercises did not appear to be barriers for these individuals. Compared to the most compliant participants, the individuals who performed the exercises < 50% of the time tended to agree more with the statement "The exercise program was too long" (mean Likert score 3.11 vs 2.43) (Table 3). Although each program was approximately 15 minutes in length, this may have been a barrier to program completion for some girls. Boredom rates with the home program appeared similar between the 2 groups. Boredom with doing the exercises at home alone may be a barrier to use of home-based programs. This further suggests the need to implement programs in a supervised, school-based setting where adolescents spend a significant amount of their extracurricular (and athletic and social) time.

One limitation of this study includes the small sample size. Of the 175 athletes who were eligible to participate, only 66 participated in the introductory meeting, and only 27 completed the follow-up survey. Obtaining parental consent and student assent during the summer months, when school is not in session, proved very challenging. Of the 66 that were provided equipment and requested to complete the home program, only 27 returned for the follow-up survey. We elected to schedule the follow-up meeting immediately before or after a volleyball practice, as many study participants also competed in volleyball. However, volleyball practice sometimes got moved to a different time, or athletes had outside responsibilities immediately after volleyball practice, such as work or duties at home, which precluded them from completing the follow-up survey. Other limitations include the lack of generalizability to other sports, and the small sample size from each school, making between-school comparisons impractical.

CONCLUSION

This study identifies barriers to compliance with home-based injury prevention programs in female high school athletes. The main reason for poor compliance was a lack of time, followed by failing to remember to do the program. Other studies have identified that higher compliance is associated with a decrease in injury rate. Due to multiple barriers to compliance with home-based prevention programs, school districts may wish to consider the utilization of other professionals, such as coaches or licensed athlete trainers, to properly implement an injury prevention program.

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A Case of Disabling Urinary Frequency and Pelvic Pain Due to Postoperative Uterine Adhesions

Paul D. Silva, MD; Sarah A. Suarez, MPAS, MS

ABSTRACT

Introduction: Dense lower abdominal adhesions are known to cause urinary frequency by restricting expansion of the bladder. However, since preoperative diagnosis of adhesions has been difficult and there are multiple other causes of urinary frequency, such patients may go undiagnosed. With the improving resolution of ultrasound, ever smaller pathologic structures may be visualized, particularly if they are considered in the differential diagnosis.

Case Presentation: To confirm the possibility that clinically significant lower abdominal adhesions may be visualized by ultrasound, we report on a patient who had developed disabling urinary frequency and pelvic pain after a cesarean section. Over a 5-year period, the patient underwent multiple diagnostic and therapeutic interventions at 2 large medical centers in multiple departments without success. Following this, a pelvic sonogram revealed a band of adhesions between the uterus and abdominal wall. Laparoscopic lysis of extensive pelvic adhesions was undertaken. Postoperatively, the patient was able to resume an active lifestyle, with good improvement in urinary frequency and pelvic pain.

Conclusion: Ultrasound diagnosis of uterine adhesions to the abdominal wall led to successful laparoscopic lysis of adhesions with significant improvement in a patient's urinary tract symptoms and pelvic pain.

INTRODUCTION

Dense lower abdominal adhesions are known to cause urinary frequency by restricting the expansion of the bladder.[1] However, since pelvic adhesions are difficult to diagnose without surgery and there are multiple other more common causes of urinary frequency, affected patients may go undiagnosed. With the improving resolution of ultrasound, pelvic adhesions may be visualized, particularly if they are considered in the differential diagnosis.[2] In order to confirm the possibility that clinically significant lower abdominal adhesions may be visualized by ultrasound, we report on a patient who had developed disabling urinary frequency and pelvic pain after a cesarean section.

CASE PRESENTATION

A 30-year-old woman presented for evaluation of chronic disabling urinary frequency and central pelvic pressure pain. She had 3 pregnancies: 1 live birth and 2 spontaneous abortions. The time of onset of symptoms was after an emergency cesarean section 5 years prior. The sensation of pelvic pain and pressure was in the area of the bladder and there also was dyspareunia. There was no dysuria or hematuria. Voiding frequency during the day was every 15 to 30 minutes depending on the fluid intake. The patient had undergone multiple diagnostic evaluations in various departments over the past 5 years, including negative urine analyses, urine cultures, gonorrhea, chlamydia, mycoplasma, wet preps, and a normal computed axial tomography urogram. Treatments had included antibiotics, dietary changes, and antispasmodics without success. There was 1 documented urinary tract infection (UTI) with *E coli* 1 year prior. Past medical history was unremarkable; the patient had not undergone any other abdominal surgeries.

Physical examination showed mild tenderness in the mid lower abdomen. A pelvic ultrasound was ordered. The transabdominal sonogram revealed a 1 x 1 cm fixed band of tissue extending from the anterior uterine fundal wall to the anterior abdominal wall superior to the bladder (Figure 1). This band appeared to fix the uterus in place even when attempts were made to displace the uterus laterally, superiorly, and inferiorly by abdominal and vaginal ultrasound probe exams; the uterus could not be made to slide away from its attachment to the abdominal wall.

The patient underwent laparoscopic lysis of extensive lower abdominal and pelvic adhesions. The superior limit of the adhe-

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Figure 1. Transabdominal Ultrasound

Image shows thick adhesion, which transfixed the uterus to anterior abdominal wall above the level of the bladder (1.5-4.6 MHz bandwidth).

Figure 2. Intraoperative Image of the Most Superior Dense Adhesion That Was Visualized on Ultrasound

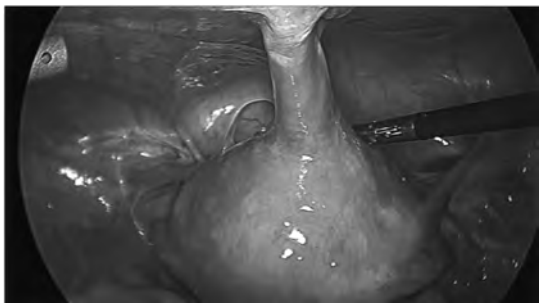
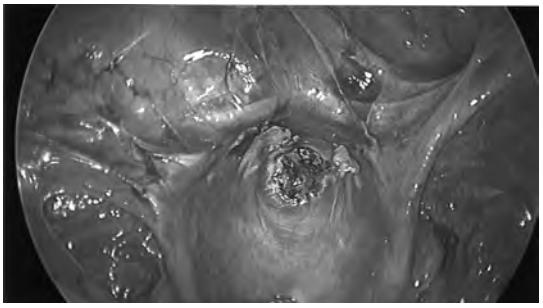


Figure 3. Uterus Returned to the True Pelvis and Bladder Serosa Revealed After Lysis of Adhesions



sions involved a 1 cm thick band of tissue extending from the uterine fundus to the anterior abdominal wall (Figure 2). Below this there were other layers of adhesions between the uterus, bladder serosa, lower abdominal wall, and pelvis. The posterior pelvis was spared of adhesions and the tubes, ovaries, appendix, and liver edge appeared normal. All of the adhesions could be lysed, freeing up the uterus from its attachments to the anterior abdominal wall and bladder area (Figure 3). Following this, the uterus noticeably retracted from its partially intra-abdominal position into the true pelvis. Postoperatively the patient's urinary complaints improved to a tolerable level. Voiding frequency was hourly without nocturia and pelvic pain noticeably improved. The patient was able to resume an active lifestyle. A postoperative pelvic ultrasound showed no evidence of adhesions.

DISCUSSION

Our patient suffered from chronic disabling urinary frequency since her emergency cesarean section. The unique aspect of our case is that preoperative ultrasound evaluation allowed for visualization of a dense adhesive band (Figure 1) that was clinically relevant as a marker of more extensive adhesions. This led to laparoscopic lysis of this band (Figure 2), as well as other lower abdominal and pelvic adhesions (Figure 3). This improved the patient's urinary frequency and pelvic pain, allowing resumption of an active lifestyle. Chen et al reported on 10 patients with intractable urinary frequency who underwent laparoscopic adhesiolysis.[1] The frequency improved in 9 of 10 cases. As in our case, 9 of 10 of their patients had varying degrees of lower abdominal pain, and 7 of 9 of these patients had improvement or resolution.

The study by Chen et al[1] was reported in 1997 and ultrasound was not used for preoperative diagnosis. This is not surprising, since at that time there was much lower ultrasound resolution capability. In recent years there have been many improvements in diagnostic ultrasound capabilities leading to greater definition of small structures. These improvements include better beam forming and image processing speed as well as improved computer algorithms for harmonics and spatial compound imaging.[3] Transducer sensitivity has improved as well as the final display resolution. We used a transabdominal probe in the current case (1.5-4.6 MHz bandwidth) and were able to clearly visualize the thickest adhesive band (Figure 1).

A recent study by Moro and coauthors showed that there was evidence of pelvic adhesions in more than one-third of women after cesarean section.[2] There was a statistically significant association between adhesions and pelvic pain, but there was not a high incidence of urinary complaints. From this study it appears that postoperative adhesions are less likely to cause urinary complaints than pelvic pain.

Uterine adherence to the abdominal wall also has been suspected by indirect ultrasound techniques. El-Shawarby et al reported on 13 women presenting with infertility and/or pelvic pain who had uterine adhesions to the anterior abdominal wall after cesarean section.[4] Preoperative ultrasound suggested adhesions in 3 of the women, in whom the uterus was noted to be

fixed to the anterior abdominal wall at the level of the cesarean section scar, while being pushed by the vaginal ultrasound probe.

Indirect methods of detection of abdominal wall adhesions by ultrasound have also been described in the general surgical literature. Sigel et al first described the viscera slide technique.[5] A normal viscera slide was observed by real-time imaging with respiratory movement or manual compression. A restricted viscera slide of less than 1 cm of the abdominal viscera relative to the abdominal wall suggested adhesions. Kothari et al described a similar technique in a prospective blinded study, which showed a significant correlation between ultrasound and intraoperative findings with regards to trocar sites suspected of having omental or bowel adhesions.[6] In our patient, the uterus could not be made to slide away from its attachment to the abdominal wall by either abdominal or vaginal compression.

Chronic urinary frequency has many causes. Neurogenic causes include stroke, Parkinson's disease, multiple sclerosis, spinal cord injury, or other central nervous system (CNS) pathology. Non-neurogenic causes include urinary tract infection, urethral diverticulum, painful bladder syndrome, vaginal atrophy, pelvic organ prolapse, abnormal voiding habits, decreased bladder capacity, increased fluid intake, diuretic use, diabetes, and idiopathic.[7]

The American Urologic Association Guidelines for evaluation of non-neurogenic overactive bladder, which includes urinary frequency, recommends a careful history, physical exam, and urinalysis. Other evaluation may be warranted including a urine culture, post-void residual, bladder diary, and symptom questionnaire. Urodynamics, cystoscopy, and diagnostic renal or bladder ultrasound also can be considered.[8]

CONCLUSION

In patients who fail conservative therapies for chronic urinary frequency, pelvic adhesions may be suspected when there is a history of cesarean section or other gynecologic surgeries.[9] Our case as well as other cases in the literature suggest that in such cases it may be worthwhile to perform a pelvic ultrasound. In this way an attempt can be made to directly visualize adhesions. If adhesions are encountered, laparoscopic lysis of adhesions may be offered for treatment. One also may find indirect evidence of adhesions through demonstrating a fixed uterus with vaginal or abdominal displacement. Since our case is the first reported case with favorable treatment results where adhesions have been directly visualized preoperatively, further cases will need to be reported to determine how often clinically relevant dense bands of adhesions can be visualized by ultrasound.

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Ectopic Thyroid Tissue With Hashimoto's Thyroiditis

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ABSTRACT

Objective: Ectopic thyroid gland is a rare occurrence with a prevalence of 1 per 100,000 to 300,000 people. Hashimoto's thyroiditis involving ectopic thyroid tissue is particularly unusual. We describe the presentation, workup, surgical management, and brief review of the literature.

Methods: Retroactive review of an 83-year-old white female patient record. As a case report, this project was exempt from institutional review board approval.

Results: We present a case of ectopic thyroid tissue located in the strap muscles with concurrent Hashimoto's thyroiditis. This tissue initially was believed to represent metastatic follicular thyroid carcinoma.

Conclusion: Whenever ectopic thyroid tissue is encountered, the gravest concern is metastatic thyroid cancer. The possibility of benign thyroid tissue should not be excluded even if the thyroid histology initially appears to be malignant in nature.

INTRODUCTION

Ectopic thyroid tissue is a rare occurrence with a prevalence of about 1 per 100,000 to 300,000 people.[1] It is even more extraordinary if Hashimoto's thyroiditis (HT) is present within that tissue; combined, they represent an ultra rare entity. To date, there are a handful of case reports demonstrating HT within ectopic thyroid tissue, but usually these are found within the normal embryological migration of the thyroid gland. In this case report, we describe a case of HT found in ectopic thyroid tissue within the strap muscles that was initially misinterpreted as metastatic follicular thyroid carcinoma. To our knowledge, the finding of extrathyroidal HT located in the strap muscles has not previously been reported.

CASE REPORT

An 83-year-old woman was referred to the Division of Head and Neck Oncology for further management of a newly diagnosed thyroid cancer. She had a past medical history of radiation in 1955 due to tuberculosis; however, radiation type or fields were unknown. Her thyroid history also was significant for radioactive iodine (RAI) ablation in 1998 for Graves' disease, resulting in post-ablation hypothyroidism. During routine examination for hypothyroidism, thyrotropin (TSH) was high at 6.95 uIU/mL and free thyroxine ($T_{4)}$ was normal at 1.57 ng/dL; an anterior neck mass was noted. An autoimmune work up was not performed. Ultrasound revealed a 5 x 5 x 4 mm hypoechoic nodule of the middle right thyroid lobe and a 4 x 3 x 3 mm calcified nodule of the inferior right thyroid lobe. Prior to detection by her endocrinologist, the patient was unaware of her neck mass and was asymptomatic. She was subsequently referred to an outside otolaryngologist.

A repeat ultrasound was obtained by the outside otolaryngologist, which revealed a 1.4 x 0.6 x 1.4 cm subcutaneous right extrathyroidal neck mass to the right midline near the hyoid bone. Computed tomography (CT) imaging demonstrated an enhancing nodule with a low attenuation center, 1 x 0.7 cm, embedded in the right strap muscle at the level of the middle right thyroid lobe (Figure 1). Just inferior to that nodule, a similar appearing enhancing nodule also was embedded in the right infrahyoid strap muscle, 1 x 0.7 cm, at the level of the inferior right thyroid lobe. A third 1.3 cm nodule with 3 mm of central calcification of the right thyroid gland also was found on CT scan imaging. The CT scan was suspicious for metastatic lymph nodes from the right thyroid gland, which were enlarged and had heterogeneous enhancement. Ultrasound guided fine needle aspiration of the 3 nodules revealed extensive infiltration of fibrocollagen stroma by

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follicular thyroid tissue, which is consistent with metastatic low-grade follicular cancer per the outside report.

Upon consultation, our pathology department reviewed the histopathologic slides. The superior nodule core biopsy revealed fragments of thyroid follicles with oxyphilic (Hurtle cell) features admixed with dense lymphoid infiltrate with adjacent normal skeletal muscle. On exam, the patient had two easily palpable masses: one measuring 1.5 cm at the level of the hyoid, and the second just about 1 cm below this mass, also to the right of the midline. The right thyroid lobe was firm on palpation. The patient then was taken to the operating room for total thyroidectomy and central dissection for possible metastatic thyroid cancer with a possibility of HT. Metastatic thyroid cancer was in the top differential due to thyroid elements found in ectopic locations. Intra-operatively, two 1.5 cm soft tissue masses were identified: one within the right sternohyoid muscle at the level of the hyoid and one at the level of the thyroid cartilage. Both thyroid lobes had smaller nodules. Surgical pathology demonstrated thyroid tissue within the strap muscles, the existence of normal thyroid tissue outside of the thyroid gland (Figure 2), and HT (Figure 3). The patient was doing well 3 months post surgery and is now scheduled to follow up as needed.

DISCUSSION

Dr Hakaru Hashimoto is the physician credited for first describing HT, which affects about 2% of the population, making it one of the most common thyroid diseases.[2] It mainly presents in young or middle-aged women, 30 to 50 years old,[3] as a diffuse painful enlargement of the thyroid gland. Hypothyroidism is its most common complication.[4] Up to 40% of patients report a positive family history of thyroid disease. HT is caused by autoimmune destruction, as evident from the presence of antithyroglobulin and antimicrosomal antibodies in the majority of patients.[3] Upon histologic examination of the thyroid glands, there is presence of fibrosis, lymphoid cellular infiltration, larger eosinophilic thyroid cells (Hurthle cells), granulated cytoplasm due to excess mitochondria, and potentially prominent nucleoli.[4] The presence of fibrosis, lymphoid cellular infiltration, and eosinophilic cells was noted in this patient.

Ectopic thyroid tissue is a rare entity occurring in about 1 per 100,000 to 300,000 people, but its prevalence increases to 1 per 4000 to 8000 in people with thyroid disease. In autopsy studies, the prevalence of ectopic thyroid tissue can range from 7% to 10%. In about 70% to 90% of ectopic thyroid tissue, it is the only thyroid tissue present.[1]

Normal embryological development of the thyroid gland starts at the floor of the primitive foregut and migrates caudally to its final position pretracheally, thereby forming the thyroglossal duct.[1] Fusion of 2 anlages makes up the thyroid gland: 2 lateral anlages and a large median endodermal anlage.[5]

Figure 1. Axial Computed Tomography (CT) Scan With Contrast of the Head and Neck

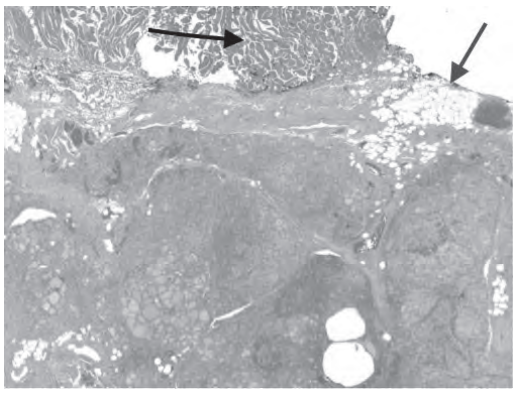
Image shows an enhancing nodule, 1 x 0.7 cm (white arrow), at the level of the thyroid cartilage, embedded in the right strap muscle with a central area of low attenuation.

Ectopic tissue is most commonly found laterally in the neck or within the migratory tract, because of a failure to complete descent. The most common location of ectopic thyroid tissue is the tongue around the foramen cecum, known as a lingual thyroid, and this accounts for up to 90% of the cases.[1] It can be asymptomatic or present with dysphagia, dysphonia, snoring, stomatolalia, etc. Patients with lingual thyroid most commonly present with hypothyroidism and without orthotopic gland, but less commonly patients may be euthyroid.[1] Even more rare, a lateral ectopic gland may be formed if the cells of the lateral anlage do not fuse with the median anlage cells.[1,5] This improper or lack of fusion is commonly found in the submandibular region. This presents as a painless mobile mass in the area of the carotid triangle or in the submandibular area. These ectopic lateral thyroid tissues are mainly right-sided and are more common in women. The patients usually have an orthotopic gland and are euthyroid.[1] Other causes of ectopic lateral thyroid gland include metastasis of thyroid carcinoma, spread of orthotopic thyroid during surgery, and displacement during embryogenesis. Other locations of ectopic thyroid include: intratracheal, intrathoracic, ovarian, gastrointestinal, and adrenal.[1]

CONCLUSION

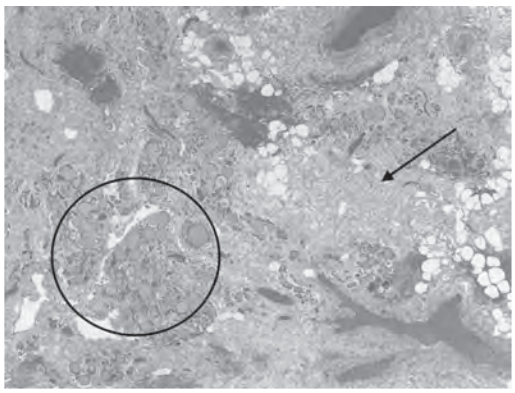
The aforementioned case reveals extrathyroidal HT found in the strap muscles of an elderly woman with an initial suspicion of a follicular neoplasm. Cassol et al wisely stated that prior to diagnosing thyroid ectopia, careful exclusion of primary thyroid malignancy needs to be performed,[2] which is what the authors in this case pursued prior to diagnosing HT. Whenever there is ectopic thyroid tissue, the convention is for excisional biopsy for

Figure 2. Hashimoto's Thyroiditis of Upper Central Neck Tissue



Abundant follicular lymphoid hyperplasia and oncocytic/Hurthle cell change of the follicles. Nearby skeletal muscle (black solid arrow) and fat (gray solid arrow). H & E stain with 2x (20 x original magnification) magnification.

Figure 3. Ectopic Thyroid Adipose and Soft Tissue



Abundant thyroid follicles (circle) within fibrous tissue (arrow) and fat (white areas) demonstrating existence of ectopic thyroid glandular tissue. H & E stain with 4x (40 x original magnification) magnification.

diagnosis. It would be difficult to differentiate a metastatic thyroid cancer from ectopic thyroid tissue. This case clearly demonstrates how methodical evaluation using ultrasound, CT imaging (to look for extension and location), histopathology, and laboratories are necessary to exclude metastatic thyroid carcinoma. The shortcoming of ultrasound imaging is that it is dependent of the operator skills, thus yielding slightly different results due to interobserver variabilities and interpretation.[6] This case, in particular, was more difficult to diagnose preoperatively due to the patient's history of prior radiation for tuberculosis and RAI ablation, which could have made histopathological diagnosis more obscure. Ultimately, total thyroidectomy was necessary due to the presumptive diagnosis of a follicular neoplasm and metastasis with a small possibility of HT. Also, it is a well-known fact that a "follicular neoplasm" is indeterminate and final diagnosis of malignancy can be confirmed only on final surgical pathology by demonstrating capsule invasion.[7] Currently there is no consensus on management strategies for ectopic thyroid due to the rarity of the condition,[1] thus it is up to the individual surgeon to formulate a proper management plan to treat the patient.

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A Case Report of Kratom Addiction and Withdrawal

David Galbis-Reig, MD

ABSTRACT

Kratom, a relatively unknown herb among physicians in the western world, is advertised on the Internet as an alternative to opioid analgesics, as a potential treatment for opioid withdrawal and as a "legal high" with minimal addiction potential. This report describes a case of kratom addiction in a 37-year-old woman with a severe opioid-like withdrawal syndrome that was managed successfully with symptom-triggered clonidine therapy and scheduled hydroxyzine. A review of other case reports of kratom toxicity, the herb's addiction potential, and the kratom withdrawal syndrome is discussed. Physicians in the United States should be aware of the growing availability and abuse of kratom and the herb's potential adverse health effects, with particular attention to kratom's toxicity, addictive potential, and associated withdrawal syndrome.

CASE PRESENTATION

A 37-year-old white woman with no previous history of substance abuse treatment was admitted to the inpatient mental health and addiction service after contacting the unit for treatment of an "addiction to kratom." The patient denied any past medical history except for postpartum depression that was partially responsive to sertraline, which the patient discontinued on her own. The patient reported that she works as a teacher and was first introduced to kratom 2 years prior to admission by a fellow teacher who was using it to treat her fibromyalgia pain. Because the patient had been in pain from recent carpal tunnel surgery and was concerned about taking opioid analgesics due to their "addictive potential," her colleague convinced her that kratom, a "nonaddictive, natural option" to "pain killers," could be a good alternative to treat her pain. She gave the patient some capsules containing dried, crushed kratom leaves. The patient reports that it provided her pain relief and also gave her a "boost of energy." Given the expense, however, she decided to purchase the concentrated extract off the Internet on the assumption that it would last longer because it would require less of the substance. Over the course of the next 2 years, the patient continued to purchase kratom extract from a single Internet site based in Florida for $150 for a 20 ml bottle labeled only with the name of the company and the country of origin (in this case Bali). The patient reported that within 6 months she realized that she was using much more of the kratom than she intended. When she attempted to cut back, she discovered that she would experience cravings as well as significant withdrawal symptoms consisting of severe abdominal cramps, sweats, blurred vision, nausea, vomiting, and diarrhea. Over the course of the next 1.5 years she attempted to detoxify in the outpatient setting with medication support from 2 outpatient providers using low dose clonidine, without success. By this point, the patient had also lost a significant amount of weight, stating that the kratom curbed her appetite. Her husband later told the physician that she was hiding the fact that she had continued to use kratom, was hiding the bottles around the home, and had gone to significant lengths to ensure that he would not discover that she had continued to order kratom online by having the product shipped to local FedEx stores. The patient admitted she was worried that she would lose her family if she did not stop taking the kratom. Despite its effects on her health (weight loss, insomnia, cravings, and decreased overall energy level) and the conflict that her use had been creating in her marriage, she had continued to take the kratom extract. Both her husband and father gave her an ultimatum to stop using the kratom, which led to her contacting the inpatient mental health and addiction unit for assistance.

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CME available. See page 53 for more information.

Figure 1. Clinical Opioid Withdrawal Scale Scores Over Time

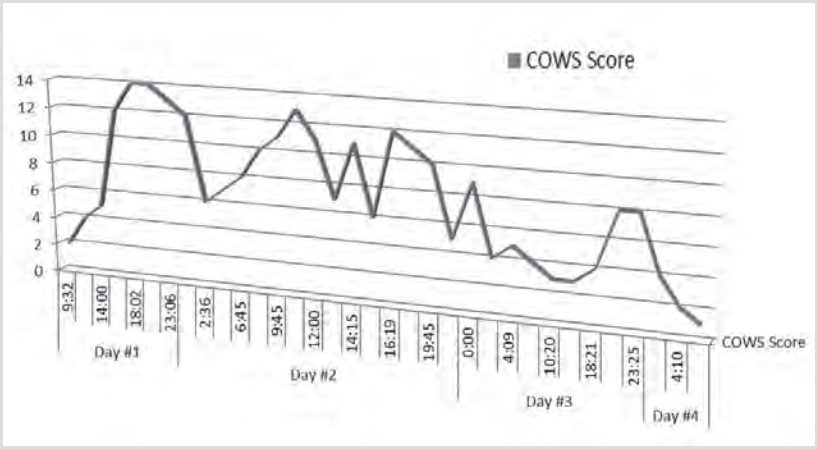
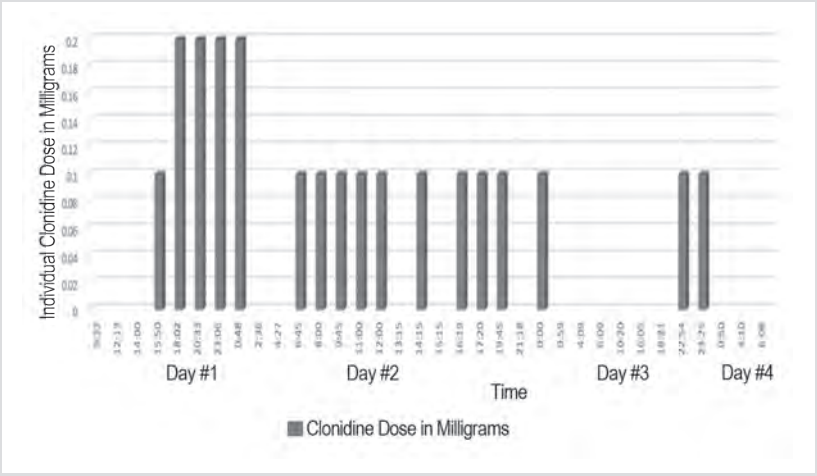


Figure 2. Kratom Withdrawal Clonidine Dose Requirements



On presentation, the patient's pupils measured approximately 2-3 mm in diameter and she complained only of mild diaphoresis. She admitted to taking her last dose of kratom at 5 AM on the day of admission. She brought her last vial of kratom, which contained approximately 2 ml of a clear fluid that she admitted was concentrated kratom extract diluted with water. Unfortunately, there was not enough of the diluted concentrate left in the bottle for laboratory analysis. The initial examination was unremarkable except for mild diaphoresis of the palms and back of the neck and significant cachexia. Electrolytes, renal function, hemogram, and liver studies were within normal limits. Urine toxicology by immunoassay was negative for all drugs of abuse including oxycodone, opioids, and methadone. A sample of urine was sent for liquid chromatography-mass spectrometry (LC-MS) to detect mitragynine (the active alkaloid in kratom), results of which came back positive at a cutoff value of 10 ng/ml. While an exact toxic concentration has not been clearly established for mitragynine, case reports suggest that side effects of mitragynine, including risk of torsade de pointes, appear to be dose dependent.[1,2] The patient was started on the opioid withdrawal protocol using symptom-triggered clonidine at a dose of 0.1-0.2 mg every 2 hours based on the Clinical Opioid Withdrawal Scale (COWS) Score, a validated scale that scores typical opioid withdrawal symptoms such as pupillary dilatation, diaphoresis, gastrointestinal distress, anxiety, fever, bone and joint pains, increased lacrimation or rhinorrhea, tremors, and yawning based on the severity of the symptoms. Scheduled hydroxyzine 50 mg by mouth every 6 hours also was started, along with a 0.1 mg per day clonidine patch to assist with withdrawal symptoms. By 1 PM on the day of admission, the patient's withdrawal symptoms started to increase rapidly as she developed myalgias, bone pain, abdominal cramping pain, nausea, and blurred vision due to rapid pupillary dilatation. The patient developed severe withdrawal symptoms by mid-afternoon, which progressed rapidly requiring up to 2 mg of oral clonidine over the next 36 hours as noted by the Clinical Opioid Withdrawal Scale (COWS) Scores (Figure 1) and frequency and dose of clonidine administered (Figure 2). Fortunately, the hyperautonomic symptoms improved rapidly over the course of 2 to 3 days. During previous attempts at detoxification, the patient described a prolonged period of severe depression and anxiety. Given the patient's previous history of postpartum depression only partially treated with sertraline, she also was started on extended release venlafaxine beginning at a dose of 37.5 mg and titrated daily up to 150 mg for her depression. In order to avoid benzodiazepines, the patient was started on pregabalin at a dose of 25 mg by mouth every 8 hours and titrated to 50 mg every 8 hours prior to discharge for her anxiety. The patient's condition stabilized over the course of 3 days in the hospital. After a family meeting with her husband and father, the patient was discharged to home with an appointment to begin participation in a dual partial hospital program. She was provided with a prescription to start naltrexone 50 mg by mouth daily for opioid antagonist therapy to begin no sooner than 7 days after discharge to avoid precipitating any additional withdrawal symptoms.

Table. Literature Review of Kratom Case Reports, Case Series, and Investigations

Authors	Number of Cases	Type of Article	Outcome	Comments
Nelson JL, et al[7]	1	Case report	Generalized tonic-clonic seizure; discharged to home	Kratom combined with Modafanil
Kronstrand R, et al[8]	9	Retrospective case series	Death	All 9 cases involved combined kratom and O-desmethyltramadol (Krypton).
Singh D, et al[9]	293	Cross-sectional survey of kratom user	Dose dependent effects of toxicity, addiction, and withdrawal	First study to measure kratom dependence, withdrawal symptoms, and drug craving.
Forrester MB[10]	14	Retrospective case series	All patients treated and recovered	Retrospective case series of kratom exposure reports to Texas Poison Centers.
Trakulsrichai S, et al[11]	52	Retrospective review series	Most cases with good prognostic outcome	Study describes toxicity and withdrawal reported to Ramathibodi Case Poison Center in Thailand.
McIntyre IM, et al[12]	1	Case report	Death	Kratom overdose; tissue samples also demonstrated mirtazapine, venlafaxine, and diphenhydramine.
Karinen R, et al[13]	1	Case report	Death	Kratom overdose; blood analysis also demonstrated citalopram, zopiclone, and lamotrigine.
Neerman MF, et al[14]	1	Case report	Death	Kratom overdose; toxicology also revealed therapeutic levels of over-the-counter cold medicine and benzodiazepine.

DISCUSSION

Kratom (*Mitragynia speciosa* Korth) is an herb indigenous to Thailand and other countries in Southeast Asia that has been used by people in that part of the world for hundreds of years to stave off fatigue and to manage pain, opioid withdrawal, and cough.[3] In the past decade, the herb has made its way around the world via Internet sales as an alternative to opioids for pain relief. Unfortunately, kratom is not well known by physicians in the United States. Kratom contains a number of active phytochemicals, but the chemical entity mitragynine (the plant's primary alkaloid) is widely regarded to produce the majority of the plant's psychoactive effects, with additional contributions from other phytochemicals, including 7-hydroxymitragynine (7-HMG) and mitraphylline.[4,5] When ingested orally, the bioavailability of mitragynine is estimated in the laboratory to be approximately 3.03% with an onset of action of approximately 5 to 10 minutes.[2] The half-life of mitragynine is not known with certainty, but its effects appear to last several hours consistent with the initiation of withdrawal symptoms within 12 to 24 hours (as occurred in the current case).[2] At low doses, mitragynine has stimulant effects, but at high doses, mitragynine behaves like an opioid and has been shown to have agonist activity at the Mu and Kappa-opioid receptors.[6] Kratom is not currently scheduled by the Drug Enforcement Agency (DEA) but is listed on its "Drugs and Chemicals of Concern" list and is sold on the Internet as a "nonaddictive" herbal alternative for pain control.[6,7] It also is used by many as a "legal high" and to assist with withdrawal from opioids. Despite its nonscheduled status with the DEA, in 2013 Wisconsin Act 351 classified kratom as a schedule 1 controlled dangerous substance, making it illegal to possess or use in Wisconsin.[8,9] Mitragynine, the primary active component of kratom, currently is being investigated as a potential analgesic with a diminished risk of respiratory depression in overdose compared to traditional opioid analgesics.[6] At the present time, however, the clinical properties of mitragynine and its potential for development as a therapeutic agent are only in the early stages of investigation.

The Internet is ripe with sites and articles that proclaim the analgesic and stimulant properties of kratom while downplaying its adverse side effects and addictive potential. Numerous case series and reports, however, have described the addictive potential of kratom, both in herbal form and as an extract. The oldest of these published articles dates back to 1975 with an early description of kratom addiction in the Thai population.[10] In a more recent study carried out to determine the risk of suicide among illicit drug users in Thailand, the investigators report that the primary drug of abuse in their study was kratom (illegal in Thailand since 1943), which was used by 59% of the 537 respondents who admitted to illicit drug use, followed by methamphetamine (24%).[11] This epidemiological study, however, did not distinguish between abuse and addiction.

More recently, a number of case series and reports of kratom toxicity have started to surface in the United States and Europe (Table). In one such report, a male patient abusing and addicted to hydromorphone attempted to use kratom to prevent withdrawal and was admitted to the hospital after he mixed the kratom with modafanil and suffered a generalized tonic-clonic seizure.[12] It is unclear if the seizure was a result of the kratom or the combination of the 2 drugs. In a separate case series from Sweden, investigators report on 9 cases of krypton intoxication and death.[13] Krypton is an herbal preparation of dried, crushed kratom leaves mixed with another mu-opioid receptor agonist, O-desmethyltramadol.[13] The abuse potential, toxicity, and withdrawal symptoms associated with kratom use have been described in at least 3 case series.[14-16] Three additional case reports also have demonstrated the potentially fatal effects of kratom without the addition of other mu-opioid agonists.[17-19]

The addictive potential of kratom (specifically mitragynine) has been well described in a discriminative stimulus rat model of addiction with properties similar to morphine and cocaine.[20] While the toxicity and addictive potential of kratom and its derivatives has not been well described in human populations, several case series and reports describe a clear addiction potential and a potentially severe, opioid-like withdrawal syndrome in humans.[14,16] Toxicity has included reports of palpitations, seizures, and coma.[12,16] The most extensive description of kratom withdrawal suggests symptoms of physical withdrawal that include myalgias, pupillary dilatation, insomnia, rhinorrhea, lacrimation, fever, hot flashes, anorexia, and diarrhea as well as psychological withdrawal symptoms that include agitation, anxiety, irritability, and depression.[14] Given the mu-opioid agonist effects of the alkaloids mitragynine and 7-hydroxymitragynine found in kratom, the symptom complex of kratom withdrawal is, not surprisingly, similar to the opioid withdrawal syndrome. The investigators of the aforementioned cross-sectional survey study declare that "kratom use is associated with drug dependence, drug withdrawal, and craving" consistent with drug addiction.[14]

Empirical evidence regarding how best to treat the kratom withdrawal syndrome and assist with long-term maintenance of sobriety from kratom is currently lacking, though the current case report suggests that a combination of high dose alpha-2 agonist therapy and hydroxyzine may provide relief from both the physical and mental symptoms of kratom withdrawal. Theoretically, buprenorphine and methadone agonist therapy also might be utilized for long-term maintenance of sobriety in kratom addiction, though kratom's current classification as a distinct chemical entity not related to the opioid class of chemicals creates some medico-legal and regulatory issues that require consideration with respect to opioid agonist therapy. As a result, and because there are no regulatory issues with antagonist therapy, the patient was prescribed oral naltrexone to assist with craving and maintenance of sobriety from kratom.

CONCLUSION

Kratom (*Mitragynia speciosa* Korth), an herb originating in Southeast Asia, which currently is not scheduled by the DEA, but is classified as a schedule 1 dangerous controlled substance in Wisconsin,[21] possesses psychoactive properties that include both stimulant and opioid-like effects. Kratom has grown, and continues to grow, in popularity in the United States and in Wisconsin. Withdrawal symptoms are mediated by the opioid properties of the plant's primary alkaloid compounds and can successfully be treated using an alpha-2 agonist and hydroxyzine as demonstrated by the current case report in which symptom-triggered clonidine therapy was utilized with COWS in conjunction with scheduled hydroxyzine. Physicians should be aware of the growing availability of kratom and its potential adverse health effects, especially its toxicity, addictive potential, and withdrawal syndrome.

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CME

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Quiz: A Case Report of Kratom Addiction and Withdrawal

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Identify the mechanisms for the addictive potential of the herb kratom.
2. Describe the symptoms of kratom withdrawal.
3. Describe various treatment modalities for kratom withdrawal.

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QUESTIONS

1. Kratom, an herb indigenous to Thailand and other countries in Southeast Asia, contains a number of active phytochemicals, but the chemical entity mitragynine (the plant's primary alkaloid) is widely regarded to produce the majority of the plant's psychoactive effects, with additional contributions from other phytochemicals, including 7-hydroxymitragynine (7-HMG) and mitraphylline.
   - ❑ True
   - ❑ False

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You may earn CME credit by reading the designated article in this issue and successfully completing the quiz (>75% correct). Return completed quiz to WMJ CME, 330 E. Lakeside St, Madison, WI 53715 or fax to 608.442.3802. You must include your name, address, telephone number and e-mail address. You will receive an e-mail from wmj@wismed.org with instructions to complete an online evaluation. Your certificate will be delivered electronically.

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2. At low doses, mitragynine behaves like an opioid and, as such, kratom use is associated with drug dependence, drug withdrawal, and craving consistent with drug addiction.
   - ❑ True
   - ❑ False

3. Although Kratom is not currently scheduled by the Drug Enforcement Agency (DEA), in Wisconsin, it is classified as a schedule 1 controlled dangerous substance, making it illegal to possess or use in Wisconsin.
   - ❑ True
   - ❑ False

4. The symptom complex of kratom withdrawal is similar to the opioid withdrawal syndrome and includes myalgias, pupillary dilatation, insomnia, rhinorrhea, lacrimation, fever, hot flashes, anorexia, and diarrhea as well as psychological withdrawal symptoms that include agitation, anxiety, irritability, and depression.
   - ❑ True
   - ❑ False

5. In the current case, a combination of high dose alpha-2 agonist therapy and hydroxyzine provided relief from both the physical and mental symptoms of kratom withdrawal.
   - ❑ True
   - ❑ False

Joseph E. Kerschner, MD

The Importance of NIH Funding to Spur Biomedical Research

Joseph E. Kerschner, MD

The National Institutes of Health (NIH) has just released its annual research funding data, which demonstrates that research is a critical economic driver in the state of Wisconsin. During the federal government's fiscal 2015, the NIH funded research projects in the state totaling $407.4 million. As importantly, each NIH dollar invested in Wisconsin generated approximately $2.21 in new state business activity, and each new research grant awarded resulted in 7 new jobs.[1]

Also in fiscal 2015, Medical College of Wisconsin (MCW) funding from the NIH increased to $87 million—continuing the institution's position as one of the leading research-intensive medical schools in the United States. In fact, MCW's was the 12th-largest percentage increase in funding of the top 50 medical schools in the country.

The impact of research funding on the Wisconsin economy underscores why the new federal spending bill, passed by Congress in mid-December, is a critical victory—not only for biomedical research but everyone in the state. The bill includes an annual funding increase of $2 billion for the NIH (from $30 to $32 billion), the first increase in more than 12 years of either flat funding or repeated cuts to the overall NIH budget, during which time it lost more than 25% of its purchasing power. This growth in funding is critical for the United States to keep pace with other developed countries in biomedical research.

> MCW and its faculty and staff are committed to helping build a brighter and healthier future for all Wisconsin residents. Developing and attracting faculty and staff who successfully build research programs to bring cutting-edge innovation to our citizens is a critical part of that process.

Since 1962, federal funding for research and development (R&D) as a share of gross domestic product (GDP) has declined from 2.2% to less than 0.5%,[2] placing the United States in 10th position by national R&D investment as a percentage of GDP among member-nations of the Organisation for Economic Co-operation and Development (OECD).[3] Still, at an annual appropriation of $32 billion, the NIH is the largest funder of biomedical research in the world.[4]

The increased funding for NIH demonstrates that our political system still is able to find bipartisan support for the country's most critical initiatives, with members of both parties agreeing that increased biomedical research is a national imperative and money spent on research now will significantly reduce the cost of health care in the future.

The federal spending bill also earmarked a $350 million increase for research on Alzheimer's disease, $200 million to the Precision Medicine Initiative, $303 million for combating antibiotic-resistance bacteria, $91 million towards programs to reduce opioid abuse, and $85 million in additional funding for the BRAIN Initiative—all of which are areas of substantial expertise at MCW. In fact, these national priorities will dovetail with many laboratories at MCW, including the following:

- Jeffrey Binder, MD, professor of neurology, and his colleagues, who are working on

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Doctor Kerschner is Dean, School of Medicine and Executive Vice President, Medical College of Wisconsin.

NIH-funded brain-related initiatives including developing new tools to improve the diagnosis and management of conditions such as epilepsy, developing functional magnetic resonance imaging (fMRI) methods for epilepsy surgery, and leading a study to ascertain why some patients with epilepsy develop memory disorders and other cognitive difficulties after surgery.

- Piero Antuono, MD, professor of neurology, pharmacology and toxicology, and director of MCW's Dementia Research Center, which is co-conducting a clinical trial for a drug to potentially treat Alzheimer's disease—an area which historically has been underfunded by the NIH. His lab also is interested in developing a resting state fMRI in aging and dementia—in particular the development of a clinically useful tool that can help in assessing different types of dementia and in subjects at risk for dementia.
- The lab of Shi-Jiang Li, PhD, professor of biophysics and director of MCW's Center for Imaging Research, which focuses on improving and developing advanced MRI acquisition and data analysis techniques to measure brain function and structural network organizations—which are used to understand Alzheimer's disease, drugs of abuse, and sedation.
- MCW's Pancreatic Cancer Program, which is undertaking an inventive phase II clinical trial to analyze the genetic profile of tumors in an effort to determine the most effective chemotherapy treatment for individual patients. This unique precision medicine trial is the first of its kind for operable pancreatic cancer, which has implications close to home—as Milwaukee's incidence rate of pancreatic cancer is 8 times greater than the rest of the country.

In addition to the NIH funding noted above, NIH dollars broadly support Clinical and Translational Science Institutes throughout the country—including a recent 5-year, $22 million Clinical and Translational Science grant received at MCW to fund the work of the Clinical and Translational Science Institute of Southeastern Wisconsin (CTSI). Using innovative mechanisms, CTSI members work to translate research discoveries more quickly into preventive, diagnostic, and therapeutic interventions for patients. Consortium members share resources, technology, knowledge, and expertise to work towards those goals. The CTSI research portfolio includes more than 185 studies, with more than 47 collaborative research studies underway. The collaborations and partnerships fostered through the CTSI already have paid off in innovation and translation of new technologies and advancements.

Recently, MCW hosted Claire Pomeroy, MD, MBA, president and chief executive officer of the Albert and Mary Lasker Foundation, who spoke on Medical Schools and Academic Health Centers: A New Outlook Toward Maintaining and Growing Their Research Portfolios. Dr Pomeroy discussed the current state of funding for biomedical research in the United States and how medical schools can thrive in today's research environment—which includes being open to innovative new partnerships, mentoring the next generation of scientists, and engaging with the public to increase support for research. All of these are important focus areas for MCW.

MCW and its faculty and staff are committed to helping build a brighter and healthier future for all Wisconsin residents. Developing and attracting faculty and staff who successfully build research programs to bring cutting-edge innovation to our citizens is a critical part of that process. Increased funding for this endeavor will be a crucial step to ensuring long-term success.

REFERENCES

1. Sources: Research America; Coalition for Life Sciences

2. Source: Budget of the US Government FY 2016, via the American Association for the Advancement of Science

3. Source: National Science Foundation, Science and Engineering Indicators 2014

4. Source: Center for American Progress, Economy Issue, March 25, 2014

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