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Special Issue: Cancer Screening

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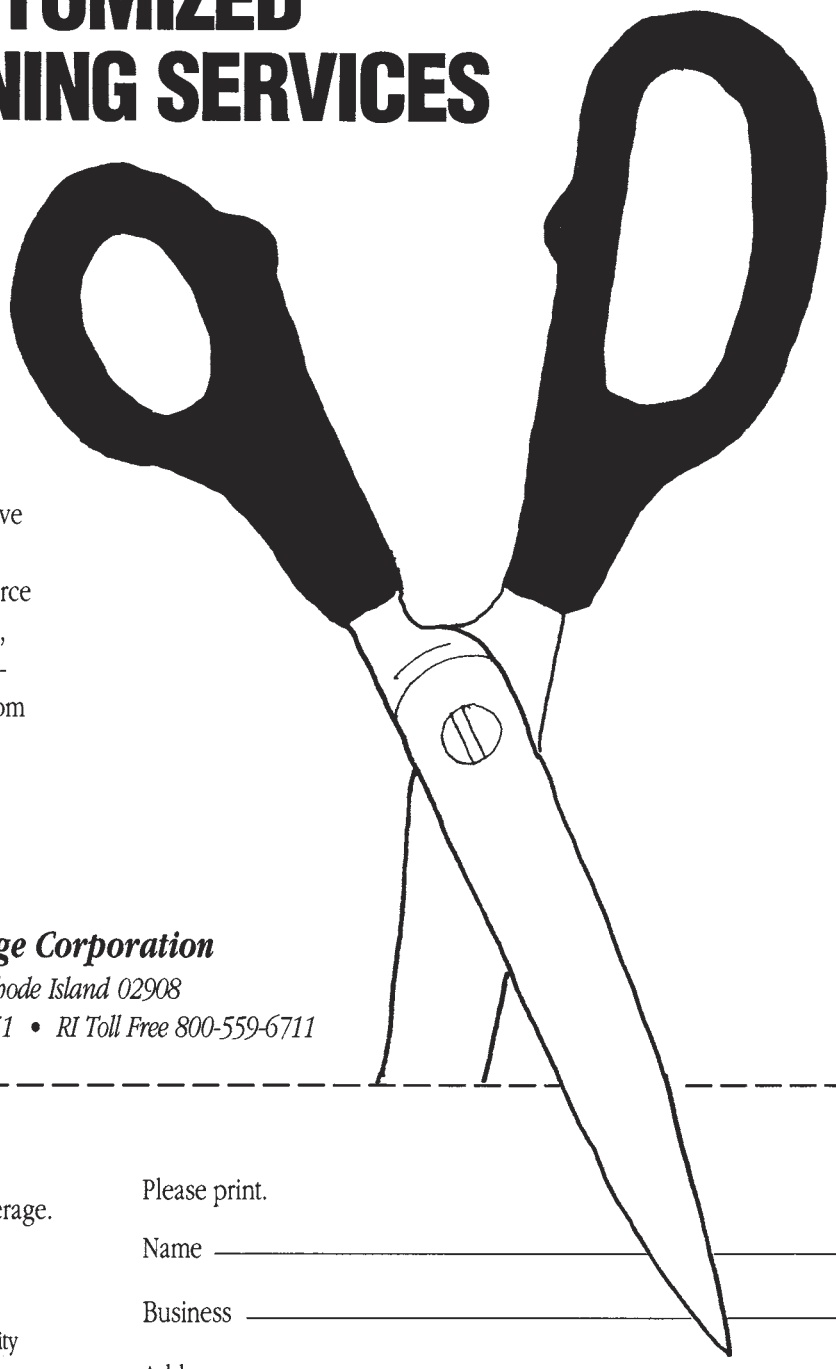

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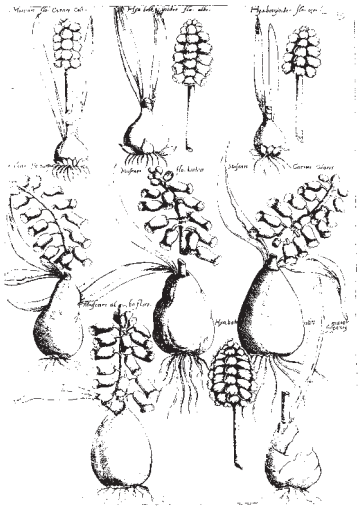
Commentaries

On Being Grandfathered



Although I feel guilty, I thank my lucky stars for being old enough not to have to be recertified as a neurologist. Since I had been grandfathered in, I didn't pay much attention to the implementation of this process, so I don't know how long ago this became a requirement to remain a bona fide, board-certified neurologist. I think it's a great idea too, which is why I feel guilty that I haven't voluntarily undergone recertification. On the one hand I figure that this is one benefit of being old, but I practice "geriatric neurology." I even participate in fellowship training programs in geriatric internal medicine, geriatric psychiatry and geriatric neurology. Who should know better than I how limited our insight becomes when we start to hear, those of us not too deaf, the tiny splashes those cortical neurons make when they drop off the surface of our brains and fall into the deep and spacious caverns we call sulci? That's probably why old neurologists don't like quiet places too much.

My guilt is many layered. I believe in quality control. Real quality control. Not the sort of quality control that JCAH requires, the "paper trail" variety where what counts is not so much the quality as the ability to fill out a form that measures something that presumably is related to quality. A signed document that confirms a meeting to discuss quality control is far better than having quality. Like everyone else in the medical community I care more if my surgeon is good than if he got his two hours of risk management CME credits. One fairly reasonable measure of his knowledge, although not his skill or judgment, is his board status, and I think most patients would feel reassured to know that she passed her recertification exam. However, I think, why should I take it and not my other elderly colleagues? More important to me is my recollection of the Neurology Board exams themselves. The number of questions that had nothing to do with clinical neurology was impressive. I later discussed this with a neurologist who helped create the test. He explained that the test was meant to discriminate passing and failing populations, and this was most easily done by asking highly technical questions that were not relevant to clinical neurology.

I have been told that recertification exams are mainly clinical and are relevant to the practice of neurology. Unlike the board exams, one does not have to know upon which chromosome each of the important mutations is located. I believe that I am a competent neurologist, for all of adult neurology, and not just for my area of focused interest. Yet I have chosen to not sign up for the exam. I am unaware of any neurologist who has voluntarily signed up either. Would it help in attracting patients? Would it be seen as a plus to publicize one's recertification? I doubt it. Once one has been in practice for a period of time, one has a reputation. A reputation is easily lost, but would passing an exam burnish it? After all, neurologists frequently do EMGs and read EEGs, yet few who do are certified in electrophysiology. And they are reimbursed the same. Yet the difference in quality does, in fact, make a difference. Many neurologists will not accept the EMG or EEG results from an unknown neurologist simply because the quality spectrum is so wide.

I guess that one reason I use to justify my not taking the exam, aside from not wanting to invest a large effort, is that I have a reputation, I work hard to keep up, and failing the exam could only hurt me while passing it would merely be expected.

When I think of my own recalcitrance in not mustering the courage to recertify myself, I contrast this with a prominent physician I was told about who taught at a prestigious medical school. He was the child of a parent with Huntington's disease, and therefore at 50% risk. Huntington's causes a triad of symptoms, one of which is an alteration in behavior and another is dementia. The doctor decided that the only objective way to prove to himself that he had continuing competency, since he didn't trust his colleagues to make an honest assessment, was to take the board exam in internal medicine every year. If he failed he would stop practicing.

I am in awe of this. I could not do it. I passed my boards, back when I had a lot more brain cells than I do now, with little room to spare. I did not, and still do not equate a high score on such an exam with any better clinical skills as a neurologist.

Now I have another concern to contend with. There is a distinct possibility that in the next decade my branch of neurology, Movement Disorders, may become a "recognized" subspecialty, along with geriatric neurology, neuromuscular neurology, dementia, stroke, etc. in which case I may "need" to pass a certification exam, although I can hope that the authorities will feel some leniency to us "grandfathers."

I believe that people like me should not be grandfathered in, but until I'm forced, I doubt that I will be voluntarily signing up to take any exams.

– Joseph H. Friedman, MD

Murder, Most Foul, In a Medical School Laboratory

Most people are content if they manage to excel in one field. Oliver Wendell Holmes [1809-1894], however, could confidently claim preeminence in the varied fields of poetry, philosophy, epidemiology and higher education. Indeed, his enduring fame as a writer [and father of an eminent juror] has obscured the fact that his daily occupation had been medicine.

Holmes underwent his medical education at Harvard and, in 1832, traveled to Europe for two further years of clinical training before returning to Boston to open his office for the general practice of medicine, on Tremont Row.

In 1842, Holmes began an epidemiological study of the events surrounding a dreadful disease called childbed fever, the principal cause, then, of maternal mortality. He concluded that childbed fever was a form of generalized sepsis, that it was contagious and that the vector of contagion was generally the contaminated hands of the obstetrical physician or midwife. [Three years later, Semmelweis, in Austria, reached the same conclusion.]

Holmes was highly regarded by his medical peers; and accordingly he was appointed as the George Parkman Professor of Anatomy at the Harvard Medical School, and, in 1847, he was selected as dean of the medical school.

His years at Harvard witnessed some wondrous events, such as the inaugural use of a general anesthetic at Massachusetts General Hospital in 1846; but there also were events that were less commendable, such as the brutal murder of Dr. George Parkman, a Harvard medical graduate, Class of 1815, and the benefactor of Holmes' endowed professorship.

Newspapers called this murder, and the subsequent trial, "the murder of the century." It attracted journalists from as far away as central Europe and threatened the stability, even the integrity, of Harvard, particularly so, since the man accused of the murder was Harvard's eminent Dr. John White Webster, Professor of Chemistry.

The victim, George Parkman [1790-1849], was the scion of a distinguished Boston Brahmin family and a philanthropist of note. His family's real estate holdings allowed Parkman to donate the land upon which the Harvard Medical School was constructed [appropriately, on Parkman Street abutting the Charles River, next to the Massachusetts General Hospital]. He also underwrote the endowment which supported Holmes' professorship.

Upon graduation from medical school, Parkman sailed to Europe; but instead of studying in England, he elected to go to France, specifically to study their radically new methods for the compassionate care of the insane. He returned to Massachusetts, vowing to devote his medical career to the establishment of a hospital, a "retreat," where the mentally afflicted might be treated more humanely.

Parkman turned his great energies, and funds, to the design and construction of a modern mental hospital, an institution which was eventually the McClean Hospital, one of this nation's outstanding psychiatric centers. Parkman's wish to become its first director, however, was denied since the hospital's trustees feared that such an appointment would represent a conflict of interests.

In bitterness Parkman turned away from medicine and concentrated his energies on the management of his father's vast realty holdings. People described him now as a tall, forbidding and autocratic man who was punctual at all times, fastidious in habit and increasingly parsimonious. Much of his income was derived from interest upon loans. And one of his many customers was Professor Webster. In stark contrast to Parkman, Webster was widely known as a gregarious soul, musically talented, witty, an imprudent spender and incapable of balancing his budget. Webster owed Parkman $2,400, and, as of November 23, 1849, could not repay his debt.

The last time that Parkman had been seen alive on that fateful day was during his walk to the medical school, where he sought out Webster in his laboratory. Some witnesses recalled hearing an exchange of harsh words. By nightfall the Parkman family, deeply distressed that he had not returned, undertook a wide but unsuccessful search.

A week went by with no sign of Parkman. An anatomy assistant at the medical school, Ephraim Littlefield, dug through one of the medical school walls to an area beneath Webster's laboratory. No reason had ever been given for this exploratory excavation; but, whatever prompted Littlefield, he nonetheless uncovered a freshly dissected torso and a few limbs. Circumstantial evidence was sufficient for the state to indict Webster for the un-witnessed murder of his colleague, Dr. Parkman. The trial began 116 days later and it rapidly became the preeminent news story in New England.

Harvard Medical School, now under the academic leadership of Oliver Wendell Holmes, was immensely distressed by the trial. Holmes was asked to testify whether the recovered torso might be Parkman's. He declared that it was consistent with Parkman's general physique. Parkman's widow, however, asserted that it definitely was her husband's body, based on her recognition of certain markings in the genital region. Furthermore, Dr. Nathan Keep, Parkman's dentist, identified a set of false teeth, recovered from the furnace near Webster's laboratory, as identical to the teeth he had made for Parkman. Thus, by the primitive forensic standards of the mid-19th Century and the damning evidence that the two men had argued, the jury found Webster guilty and he was hanged on August 20, 1850.

Harvard's president, Edward Everett, declared that the murder was "the most painful event in our domestic history." Only slowly did the academic luster of Harvard resume. Yet, even two decades later, when Charles Dickens visited Boston, his first request was to visit the room where Dr. Parkman was alleged to have been murdered.

Holmes barely survived the rancor and dismaying publicity of this celebrated murder trial. He later resigned his deanship and devoted the next few decades to an extended speaking tour away from Boston. The name Parkman persists as a street in Boston, as a professorship at Harvard, and even as a species of house wren. John Audubon, the great naturalist and close friend of Parkman, had named a species of wren [*Troglodytes parkmanii*] in his honor "as an indication of the esteem in which I hold him, and of the gratitude which I ever cherish towards him."

– Stanley M. Aronson, MD, MPH

Cancer Screening For Prevention and Early Detection of Cancer

Arvin S. Glicksman, MD, and John Fulton, PhD

When we ask a presumably well individual to submit to a procedure for the detection or prevention of cancer, it is assumed that the risk-benefit overwhelmingly is favorable to the individual and that interventions, based upon this information, can save lives. By this standard, the Papanicolou Test is universally accepted as having a very high benefit and very low risk. Over the last 50 years it has saved millions of lives. Before the introduction of the "Pap smear," cervical cancer was the leading cause of cancer deaths in women and these deaths usually occurred before the age of 50. The regular Pap examination of women who are sexually active made it possible to detect early cancer in a curable stage. Pre-invasive cancer can be removed leaving the reproductive integrity of the woman intact. Currently under investigation are vaccines targeting strains of the **Human Papilloma Virus** (**HPV**) responsible for the development of cervical cancer. The prospect of immunizing the population against HPV is an exciting new opportunity for the 21st century, but paradoxically, one which may not reduce the complexity or cost of cervical cancer prevention and screening. For example, there are many strains of HPV in the world, some of which would be "covered" by the vaccine, and others not, and infinite possibilities for HPV mutation. These facts, combined with other givens, such as less than perfect vaccine coverage in any given population, infection prior to vaccination, immigration of people from geographic areas of low vaccine coverage, and the less-than-perfect immunity afforded by any vaccine in any population, will assure the use of the Pap test (or its medical descendent) for decades to come. Nonetheless, using HPV vaccine *and* the Pap test promises to reduce disease burden substantially in developed and developing societies, alike.

While there have been occasional outbursts of statistical reviews questioning the value of mammography, there has been overwhelming support in the medical community for the value of mammography. In Rhode Island, where we have one of the highest mammography utilization rates in the country, we have seen significant down-staging of disease at presentation with a concomitant improved survival rate for women with breast cancer. In Dr. Schepps' paper, she addresses the issue of yet improving the value of mammography by newer diagnostic modalities. While *false positive* reports of mammographic abnormalities cause anxiety and apprehension for women (thus creating their own impetus for test refinement), *false negative* reports are even more concerning, given at present the still-narrow temporal window of opportunity for effecting long-lasting cancer freedom in breast cancer victims. By improving our ability to locate and biopsy lesions in dense breasts and other difficult situations, we can look forward to an improvement in both the sensitivity *and* specificity of mammography, thus both the survival benefit *and* efficiency of the test for all women.

Colorectal cancer in both men and women is the second leading cause of cancer death in Rhode Island. Identifying and removing precancerous polyps has been associated with a decrease in the number of colon resections for colorectal cancer. As Dr. Lidofsky points out, complete examination of the colon involves careful preparation, a time-consuming, inconvenient, and uncomfortable process considered odious by many. The procedure itself is invasive and some patients resist having the "gold standard" procedure, colonoscopy. Newer, somewhat less invasive procedures may overcome some of the public resistance to colorectal cancer screening while having the advantage, potentially, of fewer side effects such as perforation of the colon and peritonitis. Virtual colonoscopy, an x-ray procedure, is not widely performed and may need fine adjustments before it is "ready for prime time." As proteomic research proceeds, the identification of stool DNA associated with malignant lesions has not been perfected, but some forms of the new stool tests are now undergoing clinical trials to establish specificity, sensitivity, and patient acceptability. Notwithstanding these exciting improvements in colorectal cancer screening, the 500 pound gorilla in the room is *not* patient resistance to "things fecal," but rather the high out-of-pocket cost of colorectal cancer screening in our state. It is one thing to ask a patient to follow the distasteful and embarrassing steps associated with FOBTs and endoscopy preps. It is quite another to ask that same patient to plunk down $400 or more at the time of a colonoscopy as a pseudo-co-pay. "Pseudo-" co-pay? Yes, indeed. The accepted use of the co-pay in health care economics is to deter over-use of less-than-lifesaving services, not to deter potentially life-saving screening tests prescribed according to nationally recognized guidelines (thoughtfully developed on the basis of successful clinical trials). We think it is time to examine this practice thoroughly in open debate.

Perhaps the biggest dilemma in cancer screening is what to do with the information from a simple blood test, the PSA, for detection of prostate cancer. Doctors Cohen, Schiff, and Kelty discuss different PSA tests available and address the issue of what is "insignificant prostate cancer." On the one hand, high grade prostate cancer has been diagnosed in some young men with "normal" PSA values, and on the other hand, we continue to find a considerable a number of low grade and medium grade prostate cancers in older men who will most likely die *with, not* of prostate cancer. The dilemma with an abnormal PSA finding is whom do we biopsy and whom should we treat? For some populations

at high risk, such as African-American men, we believe that screening is *necessary* starting at age 40, despite the risk of side effects (incontinence, impotence) inherent in current treatments for prostate cancer. Other populations, at various degrees of lower risk, require different screening regimens to balance the potential benefits and costs of treatment. One thing is certain, however. As we debate what to do with PSA findings, the test is being widely used, resulting in a stage migration to more local disease. Less men are presenting with advanced disease *de nouveau,* and the death rate from prostate cancer is declining among high-risk and low-risk men, alike. Although we have a long way to go before we are comfortable in the way we utilize PSA test results, we know we are on the right road.

One of the least invasive and least frequently performed screenings is total skin examination. As Dr. Cordova and Dr. Weinstock point out, skin cancer is the *most* common cancer. It is "on the surface" and easily detected, if someone skilled in the identification of skin lesions looks for it. In Rhode Island, where many people enjoy outdoor activities associated with high-risk skin exposure, skin cancer and particularly melanoma is a high risk problem. Most primary care providers understand the importance of examining the skin, but how many do total skin examinations of high-risk (e.g., fair-skinned) individuals during annual physicals, or alternatively, assure that high-risk patients get evaluated regularly by a dermatologist? How many primary care providers are skilled at identifying squamous cell carcinoma of the skin, a deadly disease? Even malignant melanomas may be difficult to identify without special skills and considerable experience. Most skin cancers can be prevented by decreasing exposure to the sun, and since this is cumulative damage, prevention should start at a very early age. Both prevention and detection of skin cancer has not been in the forefront of the public's attention, and yet preventing skin cancer is one of the easiest interventions to effect. Awareness of the dangers of sun exposures (and tanning booths), particularly in the "Ocean State," needs to start in grade school and emphasized by teachers, parents, coaches, and everyone else involved with the youngsters who are sent out into the noonday sun to play. The US Preventive Services Task Force has not found "sufficient evidence" to recommend regular total skin evaluation for the average adult. Could this be because data on skin cancer, except for melanoma, are not recorded in tumor registries across the country? Or that many dermatologists do not believe squamous carcinoma of the skin is a problem (Dr. Weinstock is not one of them)? Awareness as adults of "cumulative sun damage" and the regular performance of total skin examination should not be a haphazard event, but should be practiced regularly, joining other effective cancer screening tests.

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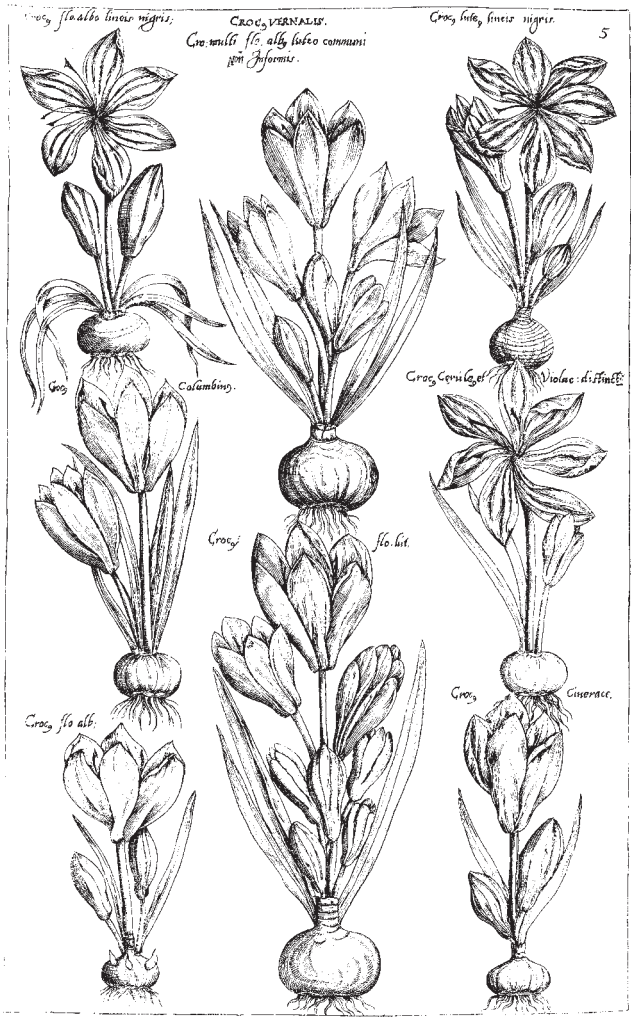


HPV Vaccines – Why Aren't They the Answer Yet?

Amy Kirkpatrick Brown, MD, MPH, and Richard G. Moore, MD

Cervical cancer remains an important public health problem worldwide, particularly in areas without effective screening programs. Even in the United States, with screening widely available, more than 12,000 new cases of cervical cancer are diagnosed annually and approximately 4,200 women die from what is an essentially preventable disease.[1] The worldwide burden of disease is significantly higher, with up to 500,000 deaths per year. Cervical cancer is the leading cause of female cancer death in many areas. Although screening programs can be effective when well-implemented, limited resources have hindered their development in many parts of the world. In addition, a significant segment of the population remains unscreened even where programs are available. In the United States in 1994, approximately 20% of women between 18-64 years old had not undergone Pap smear screening within the previous three years.[2]

The recognition in the 1980s that the **human papillomavirus (HPV)** is the causative agent for 95% of cervical cancers provided opportunities for prevention, treatment, and preventive and therapeutic vaccinations. Such vaccinations, if effective, would have a profound impact on the incidence of cervical cancer, especially in areas without effective screening programs. Several challenges remain to be overcome however prior to widespread implementation of HPV vaccination programs.

HPV Background

The human papillomavirus is a non-lytic double stranded DNA virus. There are over 100 identified HPV types, almost half of which infect the anogenital region[3]. Of these, a subset of oncogenic types have been identified.[3,4,5,6] A study by Munoz et al, identified 15 high risk and 3 probable high risk types which are associated with an odds ratio of 158 for the development of cervical cancer[7].

The HPV viral genome consists of 9 open reading frames encoding 7 early genes (E1-E7) and 2 late genes (L1 and L2). E1-E7 are responsible for viral propagation and L1 and L2 encode the viral capsid proteins. L1 is more abundant than L2, accounting for approximately 80% of the capsid[8]. The L1 and L2 capsid proteins are necessary for initial infection of the basal layer of epithelium, however, once the virion has been internalized, these proteins are no longer accessible to the host immune system. Once inside the cell, the E1 and E2 proteins initiate and maintain viral replication. It is the E6 and E7 proteins that provide the HPV virus with its oncogenic potential. E6 binds the tumor suppressor p53 and stimulates its ubiquitination and subsequent degradation, resulting in decreased apoptosis. E7 binds to the tumor suppressor pRb, leading to its inactivation and therefore uncontrolled cellular proliferation.

Since the majority of HPV infections do not result in malignant transformation, an additional step is necessary. In benign HPV lesions, the viral genome remains separate from that of the host, existing in episomal form. This allows normal transcription and translation of the E2 gene, whose product suppresses E6 and E7. In lesions with malignant potential, the HPV DNA integrates into the host genome. This integration occurs within the E2 open reading frame, resulting in a loss of the E2 protein. This loss of E2 eliminates the suppression of E6 and E7 thus allowing them to exert their effects on their target tumor suppressor genes, p53 and pRb respectively.

HPV Epidemiology and Natural History

HPV is the most common STD in the United States[3] with estimates that half of all sexually active adults have had an HPV infection[9]; the Institute of Medicine has estimated the annual cost of HPV related disease at $10billion.[10] Over 95% of invasive cervical cancers have detectable HPV DNA.[11] HPV 16 is the high risk type accounting for the largest proportion of invasive cancers, approximately half, with some geographical variation. Other common high risk types are 18, 31, and 45 and together with HPV 16, these four subtypes are detected in 80% of cervical cancer lesions.

Following infection with HPV, there is a significant lag prior to the development of cervical cancer. The success of screening programs has been due to the fact that HPV induces a series of recognizable pre-malignant lesions prior to the development of invasive carcinoma that can be successfully identified and treated. A substantial percentage of these lesions will regress spontaneously however, even without treatment, suggesting continued host immune response even after initial infection.

During this time, the natural host defenses may successfully clear the infection. Both humoral and cell-mediated responses have been shown to be important in the natural response to

Oncogenic Potential of HPV Types

High Risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Probable High Risk	26, 53, 66
Low Risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

HPV infection.[12] In one study by Ho, 72% of women with HPV16 DNA in cervical secretions developed anti-HPV16 antibodies. The mean time to seroconversion following detection of cervical HPV DNA was 8 months, and 57% of women had seroconverted within one year[13]. Another study by Viscidi showed that 40% of women with detectable cervical HPV 16 DNA were seropositive as compared to 15% of those without detectable DNA[14]. Over 5 years of follow-up, 67% of women initially HPV16 DNA positive cleared their infection, and 92% of women positive for any HPV cleared their infection. During the same time period, 14% of women acquired a new HPV infection.[15]

The natural immune response to HPV infection has also been demonstrated by the association of naturally regressing lesions with large T-cell infiltrates. Low levels of HPV specific killer T cells against E6 and E7 have been detected in both CIN3 and invasive cancer.[16] The increase in lesion progression in immunosupressed patients further implicates host defenses in the clearance of HPV infection.

General Principles of Vaccination

Broadly stated, the goal of any vaccine is to induce long-lasting immunity without causing infection. This immunity can be from the induction of cell mediated or humoral responses, or both. The majority of population based vaccines in use today are prophylactic, with the goal of preventing infection. To be effective, these vaccines must thus be given prior to exposure to the pathogen. Therapeutic vaccines on the other hand stimulate the host immune response to an already established infection. For HPV, both prophylactic and therapeutic vaccines have been developed and will be discussed in detail later.

Animal models are important in the early stages of vaccine development, and several animal papillomaviruses exist and have been used to elicit understanding of both the natural immune response to HPV infection and the effect of a variety of vaccines. The most commonly used naturally occurring animal models are the **cotton-tail rabbit papillomavirus (CRPV)**, the **bovine papillomavirus (BPV)**, the **rhesus monkey papillomavirus (RhPV)** and the **canine oral papillomavirus (COPV)**. The CRPV is probably the best characterized system, and prevention of infection following vaccination with capsid proteins as well as regression of lesions following vaccination with early proteins has been shown.[17,18] Vaccination has also been shown to successfully prevent development of papillomas caused by COPV and BPV.[19,20]

To study the human papillomaviruses in animal models, xenografts of HPV infected cells can be transferred to nude mice. Studies in such mice have been promising. Both parenteral and nasal immunizations have shown good antibody responses, with increased antibody titers in mucosal secretions following intranasal immunization[21,22]. Oral vaccine administration has demonstrated IgG and IgA responses, though at lower levels than achieved with parenteral administration[23]. Mucosal administration elicits both systemic and mucosal immune responses[24].

Prophylactic HPV Vaccines

Prophylactic vaccines against HPV would have the benefit of being able to prevent HPV infection and thus decrease not only cervical cancer incidence but also decrease the incidence of dysplastic precursor lesions. To be effective, a prophylactic vaccine must induce a response to viral antigens present on the intact virion. The capsid proteins L1 and L2 would be the natural targets of such a vaccine. Both systemic antibodies and local mucosal antibodies in the genital tract would be needed for such a vaccine to be effective. Despite much recent development, challenges to a prophylactic vaccine remain. HPV L1 IgG's are not reactive across types, and a vaccine would thus provide protection only to the type or types included in the vaccine. Given the multiple oncogenic HPV types, a vaccine that would significantly decrease the incidence of cervical cancer would have to target at least the most common types. The magnitude of regional differences in type distribution is still not entirely clear, and vaccines may need to be tailored to the region in which they are to be used[14]. The length of immunity provided by a prophylactic vaccine is also of concern. The potential exposure time to HPV is very long, essentially beginning at the onset of sexual activity. The immunity provided from a prophylactic vaccine would need to be equally long, or else booster doses would be required.

The target population for a prophylactic HPV vaccine could also pose unique difficulties compared to many existing vaccines. To ensure immunity prior to exposure, it would be necessary to vaccinate adolescents, requiring parental acceptance. Such parental acceptance of vaccination for a sexually transmitted disease cannot be assumed and has not been proven. Adolescents also do not present for medical care as often as younger pediatric patients. If life-long immunity could be provided, HPV vaccination could be added to the schedule of childhood immunizations, much as the Hepatitis B vaccine has recently been introduced. Realistic estimates of the fraction of the target population that would actually receive the vaccine must be determined before the impact of any vaccine can be predicted. An additional concern regarding the appropriate target population is the role of the vaccination of males. Although females are the subset directly affected by HPV related cervical cancer, if the prevalence of infection in males can be decreased by vaccination, the exposure to females will be further reduced. Males would also benefit directly if the low risk subtypes which are responsible for genital warts were included in a prophlyactic vaccine. It is likely this strategy would increase the appeal of vaccination to the male population. It must be also be remembered that due to the natural history of HPV infection and cervical carcinogenesis the impact of prophylactic vaccination of adolescents will not be seen for many years. As well,

the global availability and use in under-developed countries would have to be addressed.

Therapeutic HPV Vaccines

Therapeutic vaccines are designed to be given to patients already infected with HPV. This would require different antigenic targets than prophylactic vaccines, as once the virus has become intracellular the capsid proteins are no longer expressed. The E1 and E2 proteins which are expressed in cells with active viral replication would be appropriate targets for vaccines aimed at patients with early CIN[25]. The E6 and E7 proteins on the other hand would need to be targeted in vaccines directed against high grade or invasive disease where the viral genome has integrated into the host DNA and E2 is no longer expressed. One major limitation of therapeutic vaccines in patients with invasive disease is that cervical cancer is associated with some degree of immunosuppression and downregulation of HLA Class I antigen presentation. HPV derived CTL epitopes for HPV16 E6 were unable to recognize cancer cells containing HPV16 E6 due to decreased HLA expression and decreased TAP transport proteins.[26] Results in animal and clinical trials of therapeutic vaccines have been somewhat disappointing as well.[27,28]

Types of Vaccines

Several different strategies for vaccine production have been explored as options for HPV vaccines. Live attenuated or heat inactivated vaccines are not feasible for HPV vaccination due to the extreme difficulties in propagating HPV in culture.[29] Studies of the response of both animal and human subjects to HPV vaccinations of any type have been greatly facilitated by the demonstration that serum antibody titers do in fact correlate with neutralization ability.[30]

Types of Vaccines
Recombinant Vectors
Peptides
Proteins
Naked DNA
Whole virion
Virus Like Particles
Edible

Recombinant Live Vector Vaccines

Recombinant live vector vaccines are non-pathogenic or attenuated bacteria or viruses engineered to express the antigen or antigens of interest. These vaccines induce both antibody and cell-mediated immunity, often with just one dose. Multiple antigens can be expressed in a given vector vaccine, providing the potential to target multiple HPV types with a single vaccine, as well as combined prophylactic and therapeutic vaccines. Unfortunately, vector vaccines cannot be given to immunocompromised patients. This could be a significant obstacle in many areas of the developing world where the prevalence of HIV is high, and the serostatus of vaccine candidates may not be known.

A given vector can be used only once for vaccination of an individual, as prior immunization induces tolerance to the vector and prevents the desired immune response. This limitation would require the development of HPV vaccines using vectors not currently used for vaccination, or the incorporation of HPV antigens into existing vector vaccines.

Several companies and academic institutions are currently developing vector vaccines. The TA-HPV vaccine, targeting HPV16 and 18 E6 and E7 in a vaccinia vector has been shown to stimulate a good antibody response, but clinical outcomes have not yet been evaluated.[31] A combined therapeutic/prophylactic vaccinia vector vaccine is under development in China targeting HPV16 L1 and E7. Wistar has developed both adeno and vaccinia vector vaccines for HPV16 L1 and HPV16 and 18 E6 and E7 that can be administered intranasally. Both have been shown to simulate serum and vaginal antibody responses.[31] A Venezuelan equine encephalitis vector vaccine is in preclinical trials by Wyeth, and a novel vaccinia vaccine for HPV16 E6 and E7 with lysosomal targeting is in Phase I trials at Johns Hopkins.[31]

Peptide or Protein Vaccines

The main advantages to peptide and protein vaccines are their safety and low cost. The T-cell response is lessened, however, and an adjuvant is often required to stimulate inflammation. Multiple vaccine doses are required. Peptide vaccines are also limited by HLA specificity of the target epitopes.[32]

Animal studies have demonstrated good clinical responses to HPV protein vaccines.[17] The TA-GW vaccine (an HPV6 L2/E7 fusion) from Cantab has shown clearance of genital warts and decreased recurrences in Phase I and II trials in humans.[31] The TA-CIN vaccine for cervical cancer prevention is in Phase I trials[31] following successful trials in mice[33]. Other peptide and protein vaccines are being developed and tested, mostly targeted to therapeutic uses.

Naked DNA Vaccines

Bacterial plasmids can be engineered to incorporate HPV genes which can then used for vaccination. Both antibody and cell mediated responses are stimulated, and protection is long-lasting since the antigen continues to be produced. DNA vaccines are relatively cheap, and their long shelf life and stability would make them particularly attractive in developing countries where it can be difficult to maintain a cold chain. Potential risks from DNA vaccines include incorporation of the bacterial plasmid into the host DNA, although this risk remains theoretical.

Virus-Like Particles (VLPs)

Virus-like particles are formed spontaneously by the HPV capsid proteins L1 and/or L2. The discovery of this phenomenon has greatly accelerated the pace of vaccine research given the difficulties in growing intact HPV viruses in culture, and VLPs are cur-

rently the most advanced line of vaccine development. Both antibody and cell-mediated response are stimulated by VLPs, and vaccines with combinations of VLPs from more than one HPV type have also been developed. Lenz demonstrated the activation of dendritic cells by papilloma virus VLPs, resulting in a dominant T-cell response.[34] Individually, responses to L1 VLPs are type specific, although some cross-reactivity has been seen in both animal and human studies if L2 is included.[35,36,37] The VLPs alone are useful only as prophylactic vaccines, since the capsid proteins are no longer expressed once the virus has moved into the epithelial cell.

Chimeric VLPs (cVLPs) have been developed to overcome this limitation by incorporating other viral antigens inside the capsid VLP. These cVLPs provide the potential for combined therapeutic and prophylactic vaccines. cVLPs have been shown to stimulate a dendritic cell response to both the capsid proteins and an added E7 peptide.[38] Animal studies have demonstrated both regression of pre-existing tumors and protection against tumor challenge following vaccination with cVLPs.[39] One potential clinical obstacle to effective vaccination with VLPs is that although dendritic cells are activated by VLP vaccines, Langerhans cells are not, despite their internalization of VLPs.[40,41] This could theoretically limit the mucosal response to VLP vaccines.

A variety of VLPs have been studied in humans. They have consistently been safe with minimal side effects, and good antibody responses have been detected with both parenteral and intranasal administration.[42-48] A recent trial showed that 3 doses of an HPV16 VLP vaccine provided 91% protection against any HPV16 infection and 100% protection against persistent infection. The incidence of persistent HPV infection was 3.8% in controls versus 0% in immunized subjects.[49] Phase III trials with CIN endpoints, as well as with multivalent vaccines, are currently underway.

IF VACCINATION IS INTRODUCED IN A WAY THAT DOES NOT ALLOW FOR AT LEAST A REDUCTION IN SCREENING, THE COSTS MAY BE PROHIBITIVE IN MANY AREAS.

The length of immunity from VLP vaccines has not yet been determined however. In animal studies of the CRPV, titers decreased from 1:10,000 2 weeks following vaccination to 1:100 after 12 months, with concomitant decrease in clinical protection.[50] It is also not known what level of serum antibodies is required for adequate protection from infection.

Other challenges of VLP vaccines are logistical and financial. Their production is expensive, and the requirement for a cold chain could significantly limit their feasibility in developing countries, where unfortunately the need is greatest.

Plant Based and Edible Vaccines

Ease of administration and production are the obvious strengths of plant based vaccines. Genetically engineered plants can produce viral antigens, and have been shown to be capable of generating HPV capsid protein VLPs.[51,52] In mice, ingestion of a potato engineered to produce HPV antigens resulted in antibody production, although at a significantly lower level that that resulting from direct vaccination with VLP's.[51] Current work involves mostly the potato and the tomato.

Epidemiologic Concerns

The impact of any HPV vaccine on a population level will depend on several factors. First, the vaccine's effectiveness and the length of immunity induced. Second, the percent of the population at risk who actually receives the vaccine, or the vaccine coverage. Finally, the percent of cervical cancer caused by the HPV type or types included in the vaccine, known as the **population attributable fraction(PAF).** A meta-analysis has estimated the PAF of HPV16 at 27-44% depending on its prevalence in the population.[53]

A vaccine with 100% efficacy against types 16 and 18 is predicted to prevent 60% of high risk HPV infections, 46% of CIS, and 47% of invasive cancers[54]. Several researchers have modeled the impact of HPV vaccination on cancer incidence with a variety of baseline assumptions.[2,11,35,55-57] One estimate of the number of vaccinations required to prevent a single case of cervical cancer, given 90% efficacy and inclusion of the 4 most common oncogenic types, ranged from 200-350

TA-HPV	Vaccinia vector	Phase II	Cantab
TA-CIN	Protein, HPV16/18, L2/E6/E7	Phase I-II	EORTC/Cantab
???	VLP	Phase III to start 2004	Medimmune
???	Recombinant vector	Phase II	GSK
MVA-HPV-IL2	Vaccinia vector	Phase II	Transgene
FUTURE II	VLP 6,11,16,18	Phase III	Merck
???	VLP	Phase III	NCI
SGN-00101		Phase II	GOG, Institutional
???	DNA, HPV16 E7	Phase I-II	Johns Hopkins / NCI

vaccinations to prevent one cancer diagnosis[55] The possibility of serotype replacement still requires further investigation.[58] Will other serotypes increase in prevalence as those targeted by a vaccine decrease? If so, the impact on the overall incidence of cervical cancer could be blunted.

The effectiveness of the vaccine itself is not straightforward to measure, and the appropriate endpoints for clinical trials are not clear.[59] Lessons from the use of surrogate endpoints in chemoprevention trials must be considered[60] and ultimately, clinical decisions must be made on clinical endpoints. Both logistical and ethical issues must be considered in selecting trial endpoints. While the ultimate goal of vaccination is a decrease in cervical cancer, it is neither feasible nor ethical to follow patients without intervention until the development of cancer. High grade lesions have been proposed as an alternative endpoint that will both allow shorter duration studies and not put subjects at undue risk. Trials with this end point would still require several years of follow-up. Feasibility studies have attempted to estimate required sample sizes and length of follow given varying endpoints.[61,62] With a 70% effective vaccine against HPV16, 1000 subjects would be needed for an endpoint of HPV16 infection, and 15,000 for an endpoint of CIN3.[62] Acquisition or persistence of HPV DNA in cervical samples is a potential endpoint that would allow for shorter trials, although the small percent of infection that proceeds to cancer, and the lack of definitive predictive cofactors, would make it difficult to extrapolate from such a study to the ultimate endpoint of invasive cancer.

The length of immunity will also impact the ultimate effect of vaccination. The more doses that are required or the need for a booster dose will decrease overall coverage. Animal studies suggest that immunity from VLP vaccinations may be dependent on booster doses.[50] In the US and Europe the prevalence of HPV infection decreases with increasing age so some degree of waning immunity may be acceptable. Unfortunately this is not true world wide, and the populations most in need of booster doses may end up being those with the least infrastructure to receive them.

Vaccination coverage will also depend on the choice of target population, the societal acceptability of vaccination, and the infrastructure for vaccine administration. A long lasting vaccine that could be incorporated into the current childhood vaccination schedule would likely have the greatest coverage, unless societal acceptance of STD vaccination for children limits its use. A combined therapeutic/ prophylactic vaccine given to adults, while more socially acceptable, would be likely to miss a greater percentage of the population.

Finally, vaccination infrastructure will be particularly important in developing countries, where trained providers are limited and cost and cold-chain requirements could be prohibitive. The effect of vaccination on current screening programs must also be considered. As it is unlikely that any vaccine will be capable of preventing all high risk HPV infections, some screening program must remain in place. This will also be necessary to detect the small proportion of cervical cancers that are not HPV-related. The intensity of this screening will to some degree depend on the PAF of disease that the HPV types NOT in the vaccine account for. The effect of the vaccine on the prevalence of low grade lesions must be considered. If a vaccine is successful in preventing high grade lesions and cancer, but does not also decrease the prevalence of low grade lesions, current triage guidelines will need to be revised to spare patients with low grade lesions unnecessary testing and intervention. The effect of a vaccine on the ultimate prevalence of cervical cancer will also depend in part on the behavior of vaccinated women. The fewer HPV types included in the vaccine, the more important continued screening will be. If vaccinated women mistakenly believe they are no longer at risk for cervical cancer and drop out of screening programs, the ultimate impact on cancer incidence will be decreased.

The financial implications of HPV vaccination must also be considered. Since screening will not be able to be eliminated, cost savings with vaccination will come primarily from decreased treatment costs of high grade lesions and invasive cancer. If vaccine boosters are necessary, the cost savings will be reduced.

Current Clinical Trials

Several trials are underway evaluating potential HPV vaccines. Although not a comprehensive list, every effort was made to identify them.

Conclusions

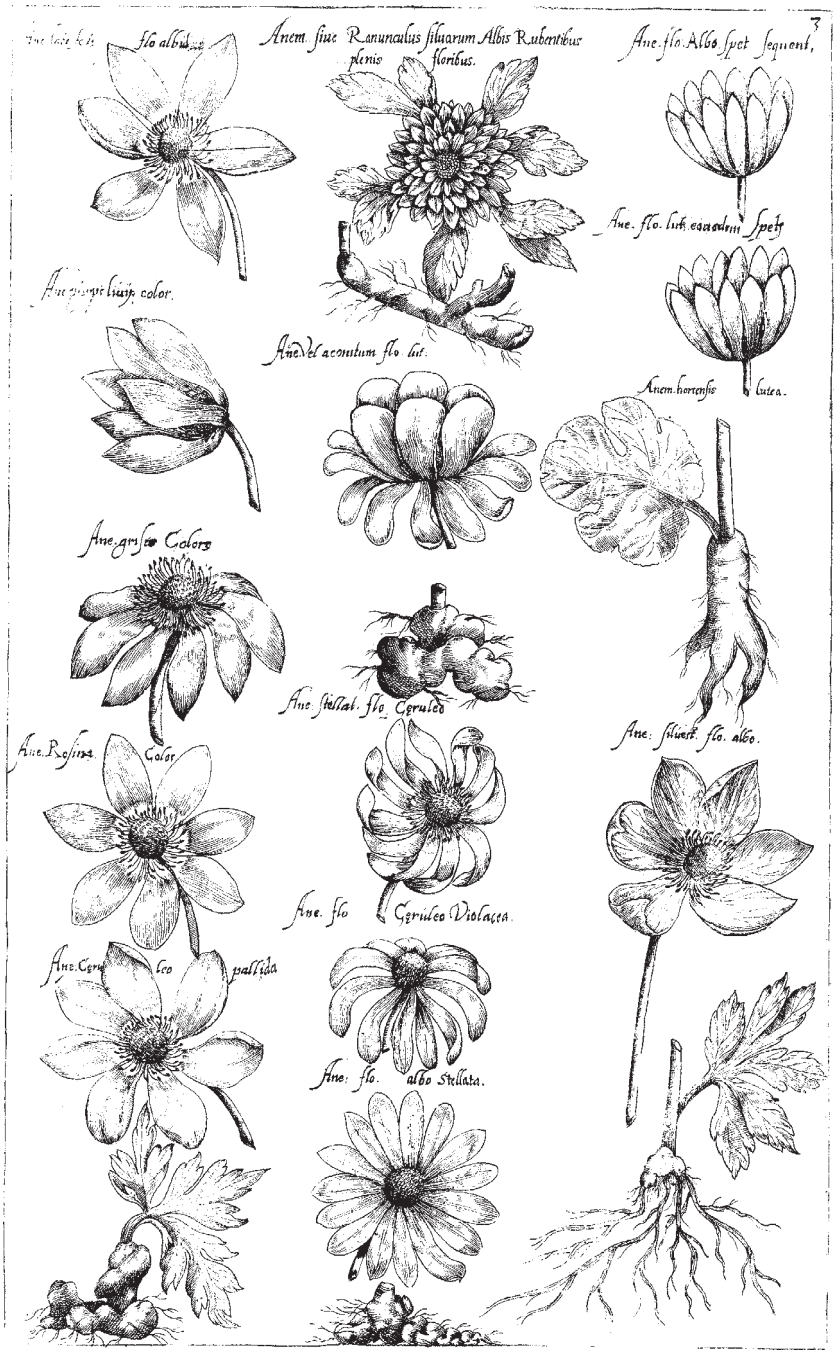
Several obstacles to the wide spread implementation of an HPV vaccine are both scientific and programmatic. Perhaps the most important scientific obstacle is the lack of definitive data on the length of immunity provided by any of the HPV vaccines currently under development. Clinical follow-up is not yet long enough to accurately determine length of protection. While serum antibody levels may be used as a surrogate marker of immunity, the levels required to provide protection against HPV infection is not clear, nor is the importance of cervical IgA levels as compared to serum IgG levels, and studies in both animals and humans have shown decreasing serum titers over time following vaccination.[50] Before a vaccine is offered to the public, we are obliged to be able to provide an accurate estimate of the length of protection such a vaccine will provide. The experience with the measles vaccine in the 1990s cannot be forgotten, where unrecognized waning immunity resulted in an epidemic of cases in adolescents and young adults.[63] If boosters are required, the population coverage will likely be significantly reduced resulting ultimately in a diminished effect on cancer incidence.

The impact on screening programs also needs to be determined prior to implementation of widespread vaccination. If a vaccine against a single subtype such as HPV16 is made commercially available, even if 100% vaccine coverage is achieved, screening programs must continue to detect the

half of cervical cancers not caused by this subtype. As well, the possible shift in viral types with excluded types becoming more prominent and resulting in an increasing number of cervical cancers. Screening programs must also continue for the millions of women who have already been exposed to HPV, even if a 100% effective prophylactic vaccine were to become available. If vaccination is introduced in a way that does not allow for at least a reduction in screening, the costs may be prohibitive in many areas. Combination vaccines to multiple types would be better able to impact both the ultimate incidence of cervical cancer and the need for screening programs, even though the development of such multivalent vaccines is not as far advanced at this time.

The societal acceptance of vaccination must also be established and decisions must be made whether to vaccinate males, and whether to include low risk people in a combination vaccine. Although this would increase the initial cost of vaccination programs, it would ultimately decrease the female exposure to the virus. It has been estimated that a prophylactic vaccine given to females only would be 60-75% as effective as if both males and females were vaccinated.[54] Education and information will need to be provided to both women and men regarding the benefits and limitations of vaccination.

In summary, although an effective prophylactic HPV VLP vaccine is likely to be technically feasible within the next several years, several questions critical to its success remain unanswered. The length of protection, the population coverage likely to be achieved, the feasibility of vaccinations in resource poor areas, and the ability to revise current screening programs, will all impact the endpoint of cervical cancer incidence. Given the numbers of women required for large scale trials with clinical endpoints, collaboration between the disparate groups working throughout the world on vaccine development is crucial. It would be both medically and fiscally foolhardy to introduce widespread vaccination before these technical and programmatic issues are addressed.



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Breast Imaging: The Role of Alternative Diagnostic Modalities

Barbara Schepps, MD

Breast cancer continues to be the highest incident cancer and the second leading cause of cancer-related death in US women. This year approximately 275,000 women will be diagnosed with the disease and 40,110 will succumb.[1] American women have a one in seven risk of developing the disease and factors such as personal history of breast or ovarian cancer, atypia, lobular carcinoma insitu or genetic aberrations such as BRCA1 or BRCA2 increase the risk for developing breast cancer. While patients with BRCA mutations comprise only about 5 to 10% of women with breast cancer, their risk for developing breast cancer is 50 to 85% .[2] The gold standard for breast cancer detection is mammography. Screening mammography, in randomized controlled studies, has been shown to decrease breast cancer mortality by 24%.[3] For each 1000 women who are screened, breast cancer is detected in 5 to 7 at first screen and two to three on subsequent regular annual screenings.

However, mammography does not identify all breast cancers. It had serious limitations in discovering tumors in women with dense mammary parenchyma and further lacks the ability to characterize lesions at screening. While many lesions can be characterized with a diagnostic mammogram, some abnormalities rely on the use of other imaging modalities and imaging-guided interventions. It is the goal of this paper to discuss the role of these alternatives.

A common misconception is that digital mammography is a different examination from film screen mammography. The digital mammogram merely employs a different image receptor; the image is acquired electronically rather than with film-screen. Although the image obtained can be viewed as film, in most practices it rarely is, but is viewed on a high-resolution computer monitor. These images can be stored electronically, eliminating the need for film, and images can be sent electronically for remote viewing. For the patient, the procedure is faster because the images are evaluated in real time and there is no wait for film processing. Most patients perceive the examination to be more comfortable. The quality of the images obtained is equal to film-screen mammography. Digital mammography is superior in assessing the dense breast because the image can be windowed and leveled for improved tissue contrast. The radiation dose is about the same, although slightly less for the patient with dense breasts.

Breast ultrasound has advanced beyond the differentiation of solid versus cystic masses with the advent of the higher frequency transducers in the early 1990s. To perform breast ultrasound, a transducer with a frequency in excess of 7.5 mHz is necessary. At this time, breast ultrasound is neither a routine screening tool nor does it replace mammography as the first line of evaluation for palpable masses except in the peripubertal patient, the patient with dense breasts with a palpable mass or in patients with metastatic disease and a negative mammogram. There are ongoing studies both in Israel and by **ACRIN (American College of Radiology Imaging Network)** evaluating ultrasound as a screening tool. To date, the variability of both equipment and operators, and the labor intensity required are substantial deterrents for using ultrasound as screening.

Ultrasound now plays a routine role in assessing palpable breast masses, characterizing mammographically detected masses, evaluating *focal* breast pain, evaluating tumor size, assessing response to neoadjuvant chemotherapy, staging the axilla of cancer patients, and for guiding interventions such as cyst aspirations or biopsies. The ability of ultrasound to characterize masses was first noted in the early 1990s when Fornage began evaluating fibroadenomas and found that the length to anteroposterior dimension of the fibroadenoma was greater than 1.4 in 86 percent and less than 1.4 in 100% of malignant tumors. [4] This was followed by a seminal article by Stavros in 1995 that evaluated 750 solid masses and extrapolated from these cases criteria to distinguish malignant from benign masses. [5] While there are limitations, theses studies were the beginning of the widespread use of ultrasound to characterize solid breast masses.

Imaging-guided biopsies have transformed the diagnosis and management of benign and malignant breast masses. With the advent of the computerized stereotactic equipment, stereotactic breast biopsies were first introduced in Sweden in 1976 and in the United States in the late 1980s.[6] Stereotactic needle-guided biopsies have been performed in Rhode Island since 1991. The stereotactic breast biopsy is a mammographically (x-ray) guided procedure that pinpoints breast lesions to within 1-2 mm. The procedure may be performed with a special table where the patient lies prone or with conventional mammographic equipment with the patient upright. Each has advantages. With the prone table there is less patient motion and less syncope, and the patient does not view the biopsy being performed. However, the add-on device for the standard mammographic unit is far less expensive and suits the low volume situation more ideally. Mammographic guidance (stereotactic biopsies) are reserved for those lesions that cannot be seen with ultrasound.

Ultrasound guided biopsies require the use of ultrasound equipment with high frequency transducers. Any lesion that can be seen with ultrasound should use ultrasound guidance to guide the biopsy to ensure that the actual lesion itself is first characterized. If the mass is a cyst, no further intervention is required unless the cyst is painful or its sonographic appearance is complex. Ultrasound guidance ensures complete aspiration of cysts. If a cyst does not aspirate completely, biopsy should be performed. Ultrasound ensures accurate sampling of both palpable and non-palpable solid masses. Even palpable lesions are more accurately sampled with ultrasound guidance.

A variety of needle systems are available to perform both stereotactic and ultrasound-guided biopsies. These range from needles of tiny caliber (FNA) to larger needles (9-14g) spring-loaded or vacuum assistance for so-called large core needle biopsies. The use of FNA is limited both because of the paucity of qualified cytopathologists and the inability to determine whether an identified tumor is invasive. The accuracy of image-guided biopsies is reported in several series to be greater than 98%.

The latest tool in the breast imaging armamentarium is **magnetic resonance imaging (MRI).** First used in 1986, its value was impaired due to insufficient standardization of the technique, lack of reproducibility and the need for intravenous contrast injection. Further requirements include an MRI unit with field strength of 1.5 Tesla or greater and a dedicated breast coils. To perform the procedure for the detection of breast cancer the equipment must also be equipped to employ high spatial and temporal resolution and create thin slices. Since the examination is restricted to the "closed" magnet, patients with claustrophobia are excluded. The exam takes about 25 minutes. Furthermore, breast MRI is highly sensitive but not highly specific, with reports of sensitivity for invasive breast cancer approaching 100%. For DCIS, reports of sensitivity range from 50 to 90%. For DCIS, MRI and mammography are complementary with mammography detecting five to 10% of the cases that are not detected with MRI because of the presence of microcalcifications.[7]

Both sensitivity and specificity depend on patient selection, MR technique, level of experience, interpretation guidelines an intimate understanding of mammographic images for correlative purposes. A variety of issues can affect MRI interpretation. MRI characteristics of benign and malignant lesions can overlap. Hormonal status of the patient can affect the image and ideally, for the menstruating patient, the exam should be performed on days six through 18 of the menstrual cycle. Hormone replacement therapy can affect the images as well. Limitations of the study include a significant false positive rate, with one false positive per 5 to 10 studies. Other limitations include the need to be able to biopsy with MRI guidance since a certain number of lesions are not detected by other imaging modalities or by physical examination. Clearly, the interpretation is dependent upon the expertise of the radiologist in reading breast MR, breast ultrasound and mammography.

THE LATEST TOOL IN THE BREAST IMAGING ARMAMENTARIUM IS MRI.

There are now numerous indications for breast MRI. It is indicated preoperatively for staging newly diagnosed breast cancer because the findings may alter the extent or type of surgery planned. It is also valuable in assessing response to neo-adjuvant chemotherapy. In patients with a history of breast cancer, it is useful in assessing post-operative residual tumor as well as for disease recurrence. Other indications include evaluating for occult tumor in patients with metastatic disease in the axilla whose mammogram, ultrasound and physical examination are negative. Breast MRI should also be used to screening high risk women, particularly those with genetic mutations such as BRCA1 and BRCA2, in women who have a first degree relative with premenopausal breast cancer, and in those women who have a personal history of breast or ovarian cancer particularly if their mammogram demonstrates dense breast tissue. In an article by Kriege et al, MRI was shown to be more sensitive than mammography in detecting tumor in women with an inherited susceptibility to breast cancer.[8] At the current time breast MRI is not indicated for routine screening, not only because of expense, but also because there is a high incidence of false positivity necessitating an increased number of biopsies. Other contraindications include the presence of pacemakers, aneurysm clips, or claustrophobia. MRI does not replace mammography as a screening tool for the general population.

In summary, mammography remains the gold standard for breast cancer screening. While ultrasound and image-guided interventions have become standard ancillary procedures in breast cancer diagnosis, MRI now begins to play an increasingly important, but limited, role in assessing for breast cancer in selected groups.

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Detection and Prevention of Colon Cancer:
Colonoscopy, Virtual Colonoscopy, and DNA Stool Tests

Sheldon Lidofsky, MD

Colorectal cancer (**CRC**) is the third leading cause of cancer and the second leading cause of cancer mortality in the United States, responsible for almost 150,000 cases and 57,000 deaths in 2003.[1] Average-risk individuals have a 5%-6% lifetime risk of developing CRC.[2] Survival is directly related to the stage of cancer at the time of diagnosis. The 5-year survival rate is 92% with localized disease; less than 60% with spread through the bowel wall; and 7% in the presence of distant metastases.[2] There is strong evidence that population-based screening can reduce the mortality from CRC by detection of CRC at early stages.[2]

Progression from normal colonic mucosa to adenomatous polyp, then early invasive carcinoma into symptomatic CRC occurs over a period of years.[3] This orderly progression offers an excellent opportunity to prevent CRC through the detection and removal of adenomatous polyps, and to decrease CRC mortality through its detection at early stages.

Evidence-based guidelines strongly recommend population-based screening for CRC.[2, 4, 5] This paper will address the role of colonoscopy, and the promising new tests of CT colonography or "Virtual colonoscopy," and fecal DNA testing, in screening for CRC.

Colonoscopy

Colonoscopy permits visualization of the entire colon directly, detection and removal of polyps, and biopsy of CRC anywhere within the colon and rectum. It requires adequate bowel preparation using laxatives or large volumes of an oral cathartic solution. IV sedation minimizes pain and discomfort. The endoscope is maneuvered within the bowel and bowel distention with air is required for adequate evaluation of the colonic mucosa. Most polyps can be removed by electrocautery techniques.

Almost 40% of CRC arise proximal to the splenic flexure.[6] Studies in patients with CRC proximal to the splenic flexure have found that a least two thirds of these patients have no CRC or adenomatous polyp distal to the splenic flexure.[7, 8] The cecum is reached in 80% to 95% of procedures.[9] Incomplete colonoscopies require either a repeat colonoscopy or supplemental barium enema to clear the proximal colon and cecum.

There are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from CRC in the average risk patient population.[2] There is, however, considerable indirect evidence of this. Data from the clinical trials of **Fecal Occult Blood Test** (**FOBT**) screening demonstrated reduced CRC mortality, with colonoscopy and polypectomy representing an integral part of the evaluation of a positive FOBT.[10, 11] There is direct evidence that screening sigmoidoscopy reduces CRC mortality.[12, 13] These studies emphasize the effectiveness of endoscopy and polypectomy, and can be extrapolated to establish the effectiveness of colonoscopy with polypectomy, which offers more complete examination of the colon.[14] The National Polyp Study demonstrated that patients who had colonoscopy with complete polypectomy had a 76% to 90% reduction in the expected rates of CRC over the subsequent 6 years and there were no deaths from CRC.[15] This reduction in expected rates and mortality of CRC occurred in a population with adenomatous polyps, a population at much higher risk for developing CRC compared to a screening population.

Colonoscopy is often referred to as the gold standard for the presence or absence of polyps and CRC.[9] Colonoscopy, however, even in experienced hands, can miss lesions. Hixson et al.[16] evaluated the miss rate of 2 colonoscopists by performing 2 consecutive same-day colonoscopies on 90 patients. They found a miss rate of 15% for polyps< 1 cm. and 0% for polyps> 1 cm. Rex ct al.[17] performed 2 consecutive same-day colonoscopies on 183 patients. The overall miss rate for adenomas was 24%, 27% for adenomas<5 mm, 13% for adenomas 6-9 mm, and 6% for adenomas > 1 cm. Patients with 2 or more adenomas at the first examination were more likely than patients with no or 1 adenoma at the first examination to have 1 or more adenomas at the second examination.

Adenoma miss rates correlated with withdrawal technique.[18] Examinations of the proximal sides of flexures, folds, and valves; cleaning and suctioning; adequate distention; and adequate exam time were important factors in achieving a lower adenomatous miss rate.

In a recent study of **CT colonography** (**CTC**), sensitivity and specificity of colonoscopy were assessed.[19] Same-day CTC and conventional colonoscopy were performed. CTC was the initial test, and lesions were reported for each segment of the colon. Colonoscopy was then performed, the colonoscopist unaware of the findings of CTC. After completing the exam of a given colonic segment by colonoscopy, the results of the CTC for that segment were revealed, referred to as segmental unblinding. If CTC revealed pathology, but that pathology was not present on colonoscopy, there was a second colonoscopic examination of that segment performed. If pathology was identified on the second examination, the colonoscopy was considered a false negative for that segment. The sensitivity of CTC for adenomatous polyps was 93.8% for polyps> 1 cm, with 96% specificity, compared to 87.5% sensitivity with colonoscopy. Most of the clinically significant adenomas missed prospectively on conventional colonoscopy were located on a fold,

especially on the backside of a fold, or near the anal verge.[20]

Colonoscopy is associated with the greatest risk of complications among the screening tests. Complications include perforation, hemorrhage, respiratory depression due to sedation, arrhythmias, ileus and nosocomial infection. Approximately 1/1000 patients have perforation, 3/1000 have major hemorrhage, and 1-3/10,000 die as a result of the procedure.[9] Serious disorders of sodium balance were reported after use of a Polyethylene Glycol colon preparation, including seizures and death.[21] Cases of hyponatremia with encephalopathy have been reported after use of Visicol tablets.[22, 23]

Expert panels recommend that colonoscopy screening be performed at 10-year intervals if the initial exam is negative.[2, 9, 18] This recommendation is based on the dwell time from the development of adenomatous polyps to transformation into CRC, estimated to be~10 years,[15] and on a case control study of screening rigid sigmoidoscopy which found a protective effect from death due to CRC for up to 10 years in that segment of colon examined.[12] However, the interval at which screening colonoscopy should be performed in average-risk persons has not been determined by observational studies. The longest reported interval between an initial normal colonoscopy and a second colonoscopy in a group of asymptomatic average risk persons 50 or older is 5.5 years.[24] Cancer incidence in this population was 0% at 5.5 years, and the incidence of adenomas with advanced pathology, defined as those> 1 cm in size, or containing villous tissue or high grade dysplasia, was <1%.

In a recent study by Schoen et al.[25] 6 of 1292 patients had CRC discovered in the distal colon 3 years after a baseline sigmoidoscopy; 72 patients had an advanced adenoma. Some of these lesions were likely missed on the baseline study because of the known inherent miss rate of colonoscopy. However, up to 15% of CRCs have microsatellite instability, associated with mutations of MMR genes. These patients may develop polyps which evolve more rapidly to CRC.[26]

Colonoscopy is one of the recommended screening tests for CRC for persons age 50 and older who are at average risk of developing CRC.[2, 4] It is the preferred screening test for persons age 50 and older who are at average risk for developing CRC as recommended by the American College of Gastroenterology.[14] It is the recommended screening test for people at an increased risk for developing CRC, including those with a family history of CRC or adenomatous polyps.[2,4,14]

Surveillance with colonoscopy is recommended for patients who are at increased risk because they have a prior history of CRC or prior adenomatous polyps, or have a disease that predisposes them to CRC, such as inflammatory bowel disease.[2, 4, 14]

Colonoscopy has been found to be cost-effective in comparison to other CRC screening strategies.[27]

CT Colongraphy (CTC). or "Virtual Colonoscopy'

CTC is a new, non-invasive method for examining the colon. Its non-invasiveness, speed of performance, lack of requirement for patient sedation, and high predictive values makes it attractive.[28]

The technique, as described by Bruzzi et al.,[28] involves the rapid acquisition of thin section CT slices of the prepared colon using a helical CT scanner, and the subsequent manipulation of data to produce 2 – Dimensional axial or 3 – Dimensional images that resemble an endoscopic view of the bowel lumen. Bowel cleansing regimens are commonly used. Residual fecal material can result in both false-positive and false-negative findings. Fecal tagging methods allow CTC evaluation in the setting of a minimally prepared or unprepared colon. Fecal tagging involves the administration of small amounts of barium or water-soluble contrast material 1 day prior to CTC. Fecal material is, therefore, labeled with high- density contrast and identified as such rather than as polyps or mass lesions.

Adequate colonic distention is required, accomplished by placement of a soft-tipped enema tube within the rectum, followed by air or CO_2 insufflation to the maximal limit tolerated by the patient. The patient is then scanned in both the supine and prone positions to redistribute the gas into segments of the colon that may have been collapsed.

Fenlon et al.[29] studied 100 high-risk patients comparing CTC with conventional colonoscopy. CTC detected 3 of 3 cancers and 20 of 22 polyps> 1cm, a 91% sensitivity. There were 19 false- positives. Sensitivities for polyps 6-9 mm and for polyps< 6mm were 82% and 55% respectively.

Pickhardt et al.[19] performed a multicenter trial involving 1201 average risk patients who underwent same day CTC and conventional colonoscopy. Stool tagging and digital subtraction, 3-D endoluminal imaging, and segmental unblinding of CTC results at colonoscopy, were performed. The sensitivity of CTC for adenomatous polyps was 93.8% for polyps at least 1 cm in diameter, 93.9% for polyps at least 8 mm in diameter, and 88.7% for polyps at least 6 mm in diameter. The sensitivity of colonoscopy for adenomatous polyps was 87.5%, 91.5%, and 92.3% for the 3 polyp sizes, respectively. Specificity of CTC for adenomatous polyps was 96.0% for polyps at least 1cm, 92.2% for polyps at least 8 mm, and 79.6% for polyps at least 6mm in diameter. Two polyps were malignant and both were detected on CTC. One of those malignant polyps was identified on colonoscopy only after the results of CTC were revealed on segmental unblinding. As well, unsuspected extracolonic malignancies were identified in 4.5% by CT findings. Pickhardt et al. demonstrated that CTC compared favorably to conventional colonoscopy in detecting colorectal neoplasms in asymptomatic average risk adults.

Cotton et al.[30] performed a multicenter study of 615 predominantly average risk patients age 50 and older referred for routine colonoscopy to assess the accuracy of CTC compared with colonoscopy. There was no stool tagging or use of 3-D rendering as a

primary review. Findings at colonoscopy were reported before and after segmental unblinding to the CTC results. The sensitivity of CTC for detecting patients with one or more lesions at least 6 mm was 39%; for lesions at least 1 cm, it was 55%. This was significantly lower when compared to conventional colonoscopy, with sensitivities of 99% and 100%, respectively. CTC missed 2 of 8 CRCs.

There is, therefore, wide variability in the sensitivity and specificity of CTC. Several factors contribute to this inconsistency, as noted by Van Dam et al.[31] First, different technologies have been used in various studies. The data suggest that multi-detector scanners allow more accurate detection of smaller lesions than single slice scanners. Hardware and software used to analyze images varies widely, as does bowel preparation methods, and the presence or absence of stool tagging. Finally, there is variation in the study populations' relative risk for neoplasia

CTC potentially offers the advantage of identifying CR neoplasms that may not be adequately identified by conventional colonoscopy. It has the capacity of imaging the colon proximal to obstructing lesions and it can serve to complete examination of the colon after an incomplete colonoscopy.

Levin et al.[32] described the limitations of CTC:

1) False positive readings in approximately15%
2) An unknown ability to detect flat adenomas, which may be a more aggressive from of neoplasia than the typical adenomatous polyp;
3) Lack of performance and training standards;
4) CTC is a diagnostic tool only, with no capability of polyp removal during the procedure;
5) The concern for cumulative radiation doses with scrial screening examinations;
6) The cost of CTC may be higher than that for conventional colonoscopy.

Van Dam et al.[31] identified fundamental questions that remain unanswered. Is there a minimum polyp size detectable by CTC for which patients should be referred for endoscopic polypectomy? What polyp size, if any, can remain in situ and undergo CTC surveillance rather that immediate polypectomy?

Fecal DNA Testing

Our understanding of the molecular biology of colorectal carcinogenesis forms the basis for detecting CRC by detection of different mutations in DNA exfoliated into the stool. Neoplasm-specific DNA mutations are released into the bowel lumen continuously via exfoliation, rather than intermittently via bleeding. DNA is stable in stool and amplification techniques, such as polymerase chain reaction allow its detection in minute amounts. The stool analysis involves the collection of an entire bowel movement. Dietary restrictions are not required before testing.

Sporadic CRC is divided into those demonstrating chromosomal instability, and those with an impaired mismatch repair (MMR) mechanism.[33] CRCs with chromosomal instability are characterized by the progressive accumulation of mutations in several genes, including the tumor suppressor genes, APC and k-Ras, and the p-53 oncogene. These constitute approximately 85% of sporadic CRCs.[33] Both pathways are associated with characteristic DNA alterations, which may be detected in stool.

Since no single mutation has been found that is expressed in all CRCs, panels of various markers are required.[33] A commercially available panel from EXACT Sciences Corporation includes 15 specific point mutations on APC, k-RAS, and p-53; gene mutations on BAT-26, a marker of microsatellite instability; and long DNA, a marker of DNA not degraded by apoptosis.[32] If any component of the panel is positive, the result is characterized as positive.

Four studies [34,35,36,37] have reported using the multi-target assay panel. Overall, 99 of the 146 patients with CRC were successfully detected by stool DNA analysis, a 67.8% sensitivity for CRC. A total of 240 patients without colonoscopic abnormalities demonstrated the presence of mutations in only 10, for a specificity of 95.8%. Brand et al.[35] demonstrated no advantage to more than 1 sample per patient for stool DNA testing. Syngal et al.[37] analyzed fecal DNA from 56 patients whose CRCs had been diagnosed at colonoscopy. A 62% sensitivity for invasive cancer was reported. Stools were also obtained following surgical resection of the primary CRC. By 6 months post- operatively, the previously found stool DNA mutations were no longer detectable.

The results in these studies in patients with adenomas>1cm in size have been quite variable, ranging from a high of 73% [34] to a low of 27%.[37]

Dong, et al.[38] were able to detect the majority of CRCs by analyzing stool DNA for just 3 genetic markers- p -53, BAT -26, and k-Ras. 51 patients who had CRC diagnosed at colonoscopy were evaluated. Prior to surgery, stool samples were collected and matched with each patient's tumor tissue. The stool was analyzed for the 3 genetic markers. Thirty patients demonstrated p-53 gene mutations in tumor DNA, and identical mutations were found in their stools. In 3 patients, mutations at the BAT-26 locus was identified in tumor, and also in each of the patient's stools. Nineteen patients demonstrated a k –Ras mutation in tumor tissue, identical to those detected in their stools. In no case was a mutation found in the stool that was not present in the primary tumor tissue.

The feasability of detecting APC mutations in fecal DNA was studied,[39] employing a novel assay called digital protein truncation.Stool samples from 28 patients with non-metastatic CRCs, 18 patients with adenomas that were at least 1 cm, and 28 control patients without neoplasm were studied. APC mutations were identified in 17 of the 28 patients with Duke's stage B2 cancer (61%), 9 of the 18 patients with adenomas at least 1 cm (50%), and in none of the 28 control patients. They concluded that APC mutations can be

detected in fecal DNA from patients with relatively early CR tumor.

Traverso, et al.[40] also demonstrated the ability of fecal DNA to detect proximal CRC. Using a method for microsatellite mutation detection, 18 of 46 proximal CRCs had microsatellite alterations detected. The identical mutations were identified in the fecal DNA of 17 of these 18 cases, with a zero% false positivity among 69 individuals with normal colonoscopies, or among 19 individuals with adenomas. This demonstrates that DNA is not degraded as it passes through the length of colon.

The American Cancer Society's CRC Advisory Group concluded that questions related to the most appropriate markers for DNA detection of CRC, on the best combination of markers, and on the results of studies in populations at average risk for CRC need to be answered before DNA stool testing can be recommended as a screening test for the average risk adult.[32]

Conclusion

The emerging competitive techniques to diagnostic colonoscopy of CTC and fecal DNA testing, though promising and innovative technologies, at this time remain unproven as screening options for the average risk population of adults who are 50 or older. These technologies should be re-visited in the near future as additional data become available.

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Colorectal Cancer Screening Resources In Rhode Island

Arvin S. Glicksman, MD

There is essentially universal agreement that timely and appropriate colorectal screening can detect and remove precancerous polyps and/or detect colon cancer in an early, curative stage. In a previous survey,[1] the Rhode Island Cancer Council found that there was uniform agreement of the gastroenterologists and surgeons who perform endoscopy and the primary care physicians that colonoscopy was the preferred procedure for colorectal cancer screening (the gold standard). Currently, approximately 50% of the population over the age of 50 have not had any test for colorectal cancer whatsoever. Some concern was expressed that if a major educational program were to increase the number of individuals seeking colorectal cancer screening, resources within the State might be overwhelmed. Accordingly the Rhode Island Cancer Council surveyed the endoscopists in the State, seeking information on the capacity of resources and their utilization. A second survey sought to determine the length of time to schedule an endoscopy appointment.

Sixty-eight questionnaires were sent to endoscopists in Rhode Island. Forty-two (62%) were returned. Ninety percent of the respondents experienced an increase in referrals/requests for colonoscopy in the last year. They reported that 80% of the patients are aware of their status as either a standard risk or being at high risk for colon cancer and they reported that 33% of the procedures resulted in finding some abnormality. (Table 1)

On average, the respondents reported performing 75 procedures per month. They believed their practices could accommodate approximately twice the number that they are performing.

The respondents all performed endoscopy examinations in a hospital endoscopy suite. In addition, a third of the endoscopists also utilized a dedicated freestanding endoscopy suite; only 10% performed endoscopies in their office suites. At no site did they report that the demand exceeded the capacity for performing colonoscopy.

On the basis of this data, an increase in the number of educational programs to improve the number of Rhode Islanders seeking this cancer screening examination can move forward without concern of overwhelming our capacity. In fact, expansion of endoscopy suites is planned at two hospitals. The availability of time that endoscopists can devote to colonoscopy may be a limiting factor in expanding the number of procedures performed. Another limiting factor may be the number of female endoscopists since many women would prefer being examined by a female endoscopist. As in most other disciplines in Rhode Island, recruiting new physicians remains a serious impediment to the delivery of health care. The Rhode Island Cancer Council is investigating other barriers to patient participation in screening colonoscopy.

Since our data would indicate that the State of Rhode Island currently has adequate facilities for endoscopy, we wished to determine how soon a procedure could be scheduled by an individual seeking referral to an endoscopists. We contacted 68 individual endoscopy offices with the following scenarios:

Table 1.

Questions	Yes	No
Increase in colonoscopies?	90.5%	9.5%
Are patients aware of risk status?	79.7%	20.3%
Colonoscopies resulting in abnormalities?	32.9%	67.1%

Table 2.

Time to Colonoscopy

	1 month	2 months	3 months
Scenario A	52%	67%	97%
Scenario B	41%	52%	98%
Scenario C	78%	96%	

Scenario A

A 63 year old woman with a family history of colon cancer (her father). She has never had any procedure before. She went to the emergency room because she thought she had the flu and the emergency room physician, after taking care of her acute problem, also recommended to her that she should seek an appointment for colonoscopy.

Scenario B

A 55 year old man who, on routine physical examination, was found to have a positive fecal occult blood test. He had never had a colonoscopy before.

Scenario C

A 70 year old man in good health with no family history of colon cancer, but was convinced by his children that this was an important test that he should have performed.

Scenario A results indicated that a person calling could have a scheduled colonoscopy within 1 month in 52%

of the offices; within 2 months in 67% of the offices; and within 3 months for 97% of the offices.

For *Scenario B*, 41% of the offices could schedule an examination within a month and 52% of the offices would schedule him within 6 weeks; 98% of the offices would schedule him within 3 months.

For *Scenario C*, 78% of the offices could schedule an examination within 1 month and 95% of the offices would schedule an examination within 2 months.

On the basis of these surveys, Rhode Island currently has adequate facilities for performing colonoscopy and individuals seeking this screening procedure would not experience an undue delay. (Table 2)

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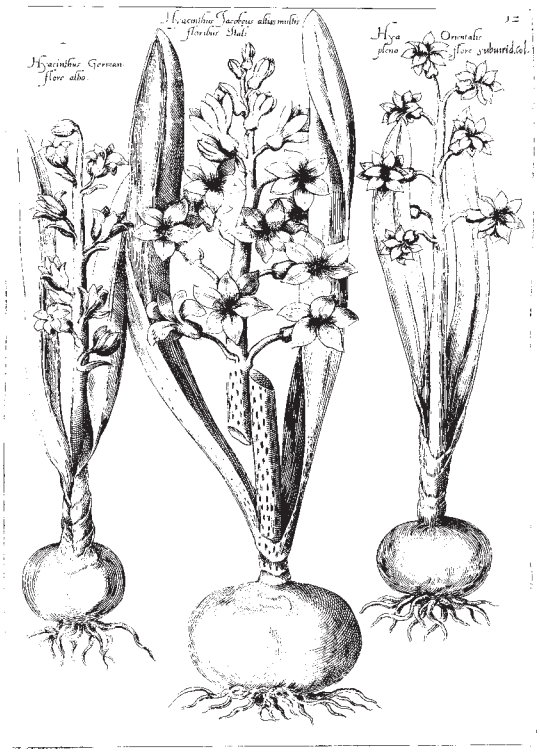

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Contributions

Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be camera-ready. Photographs should be black and white. Slides are not accepted.

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Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

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PSA Screening

Steven Cohen, MD, Stephen Schiff, MD, and Patrick Kelty, MD

The PSA screening era was born in the mid 1980's.[1,2] With the use of PSA non-palpable prostate cancer could be detected, thus, ultimately, leading to the peak detection rates of 210,000 cases per year (SEER data of 1993-95). As we have exhausted the "back-log" of undetected cancer we have returned to the baseline prevalence of prostate cancer, detecting , once again, about 180,000 new cases/ year.

Unfortunately, PSA is **prostate** specific not **cancer** specific. Recent studies, such as MTOP's work by John McConnell and Claus Roehrborn et al,[1] and Tom Stamey[2] have revealed that PSA is most closely related to prostate volume, not necessarily cancer. Additionally, in multivariate analyses used to predict prognosis, Gleason sum (histologic grade) and stage of cancer is more significant than PSA. These facts raise questions whether prostate cancers found by biopsies are found because of elevated PSA or represent clinically insignificant tumors found randomly by biopsy. A recent *New England Journal of Medicine*[3] article points out prostate cancer may exist in men with low "normal PSA". Therefore, correcting PSA for age-adjusted values reflect more prostatic size and PSA relationships (young men-small prostates, older men-larger prostates). This also allows us to be more aggressive in young men with low PSA where diagnosis and treatment may alter life expectancy compared to older men who may not benefit from aggressive therapy. Therefore "age-corrected" PSA and not " lab normal values" should be utilized. The more we learn about PSA, the more questions arise: one thing remains true, PSA is still the best biochemical tumor marker available today. It is far more reliable than CEA and CA- 125. We must learn and understand when to use and how to apply PSA clinically.

The American Urological Association guidelines recommend prostate cancer screening in men who have at least 10 years life expectancy, generally between the age of 50-75. The "fear" of legal repercussion of "failure to diagnose" is not a reason to screen men for prostate cancer. Therefore, men over 75 years old and men with less than 10 years life expectancy should not be screened. Early prostate cancer detection is unwarranted, not cost-effective, may lead to harmful interventions and will not impact longevity, High risk men (African-American and those with hereditary or familial links) should start screening at age 40.

Ever since the introduction of PSA, efforts have focused on increasing the accuracy of the test in the context of early detection of prostate cancer. Elaborated only from the ductal epithelial cells of the prostate, PSA is an excellent tool for monitoring disease status following radical prostatectomy. Postoperatively, serum levels should become undetectable unless there is persistent or recurrent disease. However, when PSA is used as a cancer screening tool with an intact prostate, the lack of specificity and sensitivity hampers its effectiveness.

PSA values of up to 4.0 ng/ml have been considered "normal;" however, recent studies have suggested 15% of patients with so-called normal PSA may have prostate cancer and a small percentage of those may harbor high grade disease. Consequently, there is also interest in improving the sensitivity of the PSA test to reduce the prevalence of false negative tests.

PSA values in the 4 to 10 ng/ml range are considered to be in the "grey zone" with 60-75% of these men having negative biopsies. Refinements in the PSA test will go a long way to improve the diagnostic accuracy for these patients.

PSA is a protease and the proteolytic activity in the blood stream is inhibited by the formation of complexes with serine protease inhibitors. Most PSA is bound and only a small portion is unbound, or "free." Most PSA is bound to ACT (antichromtrypsin). It is widely accepted that in patients with prostate cancer, more PSA is in the PSA-ACT isoform and in healthy men with benign prostatic disease, there is a greater proportion of fPSA (free PSA).

Many studies have demonstrated improved specificity utilizing the ratio of total to percentage free PSA, with values of free PSA greater than 26% more likely associated with benign disease. This calculated ratio is a useful test to help reduce unnecessary biopsies after previous negative biopsies and continued elevation of total PSA.

Recognizing that PSA complexed with ACT is seen in a higher proportion of men with prostate cancer has led to intense efforts to develop sensitive assays to detect PSA-ACT in an effort to further increase the accuracy of PSA testing. Some studies have shown complexed PSA to be equivalent to total PSA while others have shown it is better. However, technical difficulties with cross reactivity and questions about clinical usefulness remain.

There is great interest in improving the accuracy of PSA testing, which could reduce the number of unnecessary biopsies and increase the predictive value of PSA. There is active interest in the lower ranges of PSA in an effort to maximize the detection of prostate cancer. This lower range will include many men without cancer and the enhanced specificity of the complexed PSA may allow those who are truly cancer free to avoid biopsy.

Ongoing research continues to refine the role of PSA and its various forms in an effort to improve the accuracy of prostate cancer early detection. Critics claim, with merit, that this lack of specificity leads to many unnecessary prostate biopsies. In a patient with an abnormal PSA, cancer is found in only 25-33% of cases. This means that 67-75% of prostate biopsies are "unnecessary" since benign tissues are found.

Due to this lack of specificity, in-

vestigators have been trying to clarify the use of PSA by using various modalities such as PSA velocity, PSA density, and free/total PSA ratios. None of these various derivatives have decreased the number of negative prostate biopsies;i.e., the specificity of PSA in differentiating benign disease from cancer did not change significantly. Despite its usefulness, there are serious limitations in the use of PSA as a screening tool. This has led to the search for better tumor markers, which are more specific for cancer while maintaining sensitivity.

One experimental marker is **prostatic specific membrane antigen (PSM).** This is a protein located on the plasm membrane that is expressed higher in prostate cancer cells than in benign cells. The use of PSM as a marker has a sensitivity and specificity of 58% and 47%, respectively. The main drawback with this marker is that it is found via RNA samples in the serum. It is detected via reverse transcriptase amplification. When used in conjunction with PSA, it has not offered a greater specificity.[5]

Another marker being investigated is **alpha-methylacyl coenzyme A racermase** (AMACR). This protein is expressed in higher amounts by prostate cancer cells. It can be found in prostatic secretions and in the urine after a prostate biopsy. The drawback of this marker is that it was found in the urine of patients who had just recently had a prostate biopsy; however, 86% of men with prostate cancer on biopsy did express AMACR in their urine. Thus, this marker would not decrease the amount of initial negative prostate biopsies. One potential use for this marker may be to stratify patients with initial negative prostate biopsy in the face of a rising PSA. At this point, many of these patients require repeat prostate biopsies. The use of AMACR in the voided urine after the initial biopsy may help determine who truly has benign disease and who has a greater chance of having a malignancy and needs a repeat biopsy.[6]

One of the more interesting and promising approaches is the use of **artificial intelligence** (**AI**) and neuronal networks in the screening of prostate cancer. In the most recent study, investigators analyzed serum proteomic streams generated by high resolution mass spectroscopy by using a pattern recognition algorithm. After initial training of the pattern recognition program, the serum samples of men with PSA in the 2.5-15 range were examined to try and differentiate between cancer and benign disease. The model used in this study yielded a sensitivity of 100% and a specificity of 67%. What this means is that the use of this method would obviate the need for prostate biopsies in 67% of men with elevated PSAs, while no cancers would have been missed. Further testing is needed to determine if this data can be reproduced, but this is certainly one of the more promising methods to increase the specificity of prostate cancer screening.

...MEN OVER 75 YEARS OLD AND MEN WITH LESS THAN 10 YEARS LIFE EXPECTANCY SHOULD NOT BE SCREENED.

Despite a decrease in prostate cancer deaths since the use of PSA, the screening for prostate cancer remains controversial. The use of PSA and how to properly use it is at the center of this controversy. Although it remains the most sensitive and useful tumor marker available today, it has limitations, particularly in its lack of sensitivity. The use of various PSA derivatives and the search for newer tumor markers have had mixed results, which further fuels this controversy. Future efforts in redefining the role of PSA in benign and malignant disease, the use of newer markers, and the use of intelligent technology will, we hope, decrease the unnecessary biopsies and the controversies surrounding the screening for prostate cancer.

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Skin Cancer Prevention and Detection—melanoma and beyond

Katharine B. Cordova, MD, and Martin A. Weinstock, MD, PhD

Skin cancers are the most common malignancy in humans.[1] Despite recent educational campaigns and advances in medical knowledge, the incidence of **keratinocyte carcinomas (KC)** and melanoma continues to increase. KC refers to **basal cell carcinoma (BCC)** and **squamous cell carcinoma (SCC)**, the two most common types of skin cancer. BCCs and SCCs arise from keratinocytes and occur with a relative frequency of 4:1.[2] KCs rarely metastasize and can generally be cured with outpatient procedures. However, if left untreated these tumors can cause significant disfigurement, local destruction, and sometimes, but not often, death. National reporting of KC is imprecise, but the most recent figures from the American Cancer Society estimate over one million cases will be diagnosed this year.[3]

Melanoma is the most serious form of skin cancer. Of all reported cancers in the United States, melanoma ranks fifth and seventh in incidence among men and women respectively. The incidence continues to rise and an estimated 55,100 new cases will be diagnosed in 2004 with 280 in Rhode Island.[3] Approximately half of all melanomas affect people younger then 55 years of age –and deaths from melanoma occur at a younger age then most other cancers.[4] Although the mortality rates for melanoma have stabilized in recent years, an estimated 7,910 people will die from the disease in 2004.[3]

A combination of inherent host factors and exogenous environmental influences interact to develop these malignancies. Patients with more then a hundred nevi, atypical nevi, congenital nevi, a personal or family history of melanoma, or a personal history of KC are at greater risk for melanoma development. Fair skinned individuals with light eyes and poor tanning ability are more likely to develop skin cancer then their dark skinned counterparts. However, African Americans are more likely to die from the disease once diagnosed.[3] Additionally, rare genetic syndromes that impair the body's ability to repair UV-damaged DNA are associated with early and severe onset of melanoma and KCs.

Sun exposure is the major modifiable environmental factor for all types of skin cancer. In addition to overall quantity, the pattern and timing of UV exposure also appears relevant. Whereas the most common variants of melanoma are associated with intermittent, intense periods of UV exposure, SCC development seems to reflect a more chronic, cumulative exposure pattern. Reports on BCC are mixed, with some reporting intermittent rather than cumulative sun exposure to be more influential.[5] Childhood exposure and sunburns seem particular important. People with five or more severe sunburns in childhood are estimated to be at twofold greater risk of developing melanoma.[6] Higher rates of melanoma are also found in people living (or who have spent their childhood) near the equator where UV exposure is the most intense. Artificial sources of ultraviolet radiation such as tanning beds and UVA with psoralen have also been associated with increased melanoma and KC development.[7,8]

Additional environmental risk factors for KC include exposure to ionizing radiation or certain chemicals, chronic immunosuppression, smoking, arsenic ingestion, and chronic oral corticosteroid use. Transplant and immunosuppressed patients are at particularly high risk for SCC development. SCCs in transplant recipients develop earlier and are more aggressive; these patients should be closely followed by dermatologists.

Detection

"What about this spot"

Many patients present with concerns about a new "bump" or "spot." Obtaining a focused history about the presentation, evolution, and symptomatology of lesions may assist with diagnosis and clinical decision-making. Reviewing past medical history with emphasis on personal and family history of skin cancer, evaluating for immunosuppression, and examining for nevi, helps to stratify patients into relatively high or low risk categories.

Keratinocyte Carcinomas

Of all skin cancers, BCCs are the most common. The majority (80%) occur on the head and neck with the remainder primarily found on the legs and trunk.[9] BCCs are subcategorized according to clinical morphology and histopathologic findings into nodular, superficial, pigmented, or morpheaform varieties.

The classic, nodular variety has a characteristic morphology that is relatively easy to identify and diagnose on presentation: it may be a "pearly" papule, often with translucent stroma, and it may present with a rolled border, central crust, and/or telangiectasia. There may be a history of spontaneous bleeding of the lesion. Although slow growing, the potential for local destruction is significant if left untreated, especially when located near eyes, ears, nose and lips. Incidence increases with advancing age.

Superficial BCCs resemble eczema or a local area of irritation, but have more distinct margins and upon close examination, pinpoint erosions may be appreciated. They are typically on the trunk and are slow growing tumors. Pigmented BCCs may have a speckled or more diffuse pigmentation, but also may contain areas of pink or waxy skin. Their clinical presentation can resemble melanoma.

The most aggressive form of BCC is the morpheaform or sclerosing variety. These tumors account for 5% of all BCCs and often resemble a scar or

area of sclerosis with ill-defined borders.[9] Sub-clinical infiltration is common and these patients are often referred to a Mohs surgeon to ensure clear margins and minimize recurrence potential.

SCCs, although readily visible, may present a diagnostic challenge and frequently need biopsy confirmation. They present as a pink to red papule often with an overlying crust or scale and varying degrees of induration. These lesions may arise *de novo* or develop from precancerous pink lesions with adherent scale termed actinic keratoses. In addition to sun exposed areas, SCCs also develop in chronic scars, prior burn sites, ulcers, sinus drainage tracts, or mucous membranes. SCCs in these less common locations, as well as large, deep, or high grade varieties have a greater propensity to metastasize. The lip, ear, and genitalia are also high risk sites for SCC. SCCs account for the majority of deaths from nonmelanoma skin cancer.[10]

Pigmented Lesions

Melanomas are sub-classified according to clinical and histological features. The typical nodular melanoma is a brown, black, or pink papule or nodule. Superficial spreading melanoma, the most common form of melanoma, is typically a flat or minimally elevated irregularly pigmented lesion that grows radially prior to developing a vertical growth pattern. Lentigo maligna melanoma most commonly presents as an asymptomatic brown or black macule with irregular borders and is classically seen on the chronically sun exposed skin of the elderly. Acral-lentiginous melanoma typically appears as a tan to darkly pigmented lesion on the fingers, palms, or soles. This is the most common form of melanoma seen in dark skinned individuals and is often detected in a more advanced stage.

Given the considerable variation in clinical presentation, evaluation of pigmented lesions can be daunting. Many benign, pigmented lesions can mimic melanoma and distinguishing the harmless from the harmful can be difficult for even the most practiced eye. Thus, treating physicians typically maintain a low threshold for biopsy. As a result, a significant number of benign lesions are removed or sampled. This cautious approach recognizes that the most important prognostic indicator of all melanomas is depth of invasion at time of diagnosis. Melanomas less than 1 mm in thickness have an estimated ten-year survival rate of 88-96%.[11,12] As the depth increases, the survival rates drop precipitously. Maintaining a high level of clinical suspicion aims to reduce mortality by detecting and removing melanoma at an early, curable stage; complete removal of *in situ* lesions and many other early lesions is both treatment and cure.

MANY BENIGN, PIGMENTED LESIONS CAN MIMIC MELANOMA AND DISTINGUISHING THE HARMLESS FROM THE HARMFUL CAN BE DIFFICULT FOR EVEN THE MOST PRACTICED EYE.

The ABCD rule is frequently used by physicians and taught to patients to help recognize potentially malignant lesions. Identifying *a*symmetry, irregular *b*orders, *c*olor variation, or *d*iameter greater then 6mm should raise clinical suspicion. However, studies evaluating the ABCD guidelines report a sensitivity of only 65-80%.[13,14] Therefore, many clinicians have advocated the "new or changing mole" message as an easier, more inclusive tool for early melanoma identification.[15] A patient friendly booklet from the American Cancer Society entitled "Why you should know about melanoma" (American Cancer Society, 2004) emphasizes that a change in size, shape, or color of spots on the skin is the most important warning sign. By using a more general, easy-to-remember message there is hope for greater patient awareness and earlier detection of melanoma.

In recent years, many dermatologists have adopted dermoscopy as an additional diagnostic tool. By magnifying and viewing the lesion with polarized light or with liquid interface on the skin surface, hand-held devices allow visualization of morphological features not apparent to the naked eye. For physicians with formal training, use of dermoscopy reduces the number of lesions submitted for biopsy and improves clinical accuracy.[16-18] Use of this tool by untrained or inexperienced examiners, however, is not effective.[18]

Skin Cancer Screening

Many patients see dermatologists for routine skin checks. This probably reflects a combination of factors: public health campaigns have raised awareness about skin cancer, time restraints limit patient-doctor interactions to the most pressing issues, and the fragmentation of healthcare provision amongst specialists forces many patients to see a different doctor for each aspect of their healthcare. In patients considered to be high risk for melanoma, routine screening by dermatologists may result in earlier detection and excision of melanomas.[19-21] However, most melanomas do not occur in high-risk individuals; therefore; early detection efforts must be extended to the general population.[22]

Because the majority of the population visits a primary care clinician at least every two years, these clinicians are ideally suited to teach patients about skin cancer and perform initial screenings.[23] Despite evidence that physicians believe all patients should be counseled about sun protection strategies and confirmation that these interactions positively impact patients' skin cancer prevention practices, the rate at which physicians counsel about skin cancer prevention methods is quite low (e.g. 29% sunscreen, 6% other sun protection measures).[24,25] In addition to time constraints, primary care physicians have cited lack of confidence as

a significant barrier to the practice of skin cancer screening and prevention counseling. This suggests that continuing medical education programs may prove valuable. Even a brief (2-hour) seminar teaching clinicians an 8-step algorithm to triage patients with skin lesions into categories of "Act," "Reassure," or "Track" was found to improve their confidence, skills, and practices.[26]

In addition to physicians, patients and their families are encouraged to be active, engaged participants in their own care. Teaching and promoting performance of monthly self-skin examinations has become more frequent in dermatology practices. This is especially aimed toward individuals with risk factors for melanoma development. Although a case-control study suggested monthly self-skin exams could reduce melanoma mortality by 63%, few patients perform these exams in a deliberate, systematic manner.[27-29] Factors found to be key predictors of performing thorough self-skin exams included partner participation, access to a wall mirror, and a recommendation by a physician to do so.[29]

One constraint on both research and advocacy efforts is the limited evidence of efficacy and effectiveness of routine thorough self-skin exams. Although supported by the American Cancer Society, American Academy of Dermatology, and Skin Cancer Foundation, the US Preventative Services Task Force finds insufficient evidence to advocate for self-skin examinations. However the relative costs of encouraging healthy self-assessment practices seem few.[22]

Regardless of who is examining the skin, a methodical approach is key. Establishing a consistent order of examination enables detection of subtle lesions and ensures complete review of the entire skin surface. Controlling environmental factors such as lighting, patient positioning, and removal of clothing also promotes effective, thorough exams.

A recent review of KC associated deaths in Rhode Island found over half of them to be related to genital carcinoma. While men are more likely to die from non-genital SCC, in women the ratio was reversed: women were three times more likely than men to die from genital skin cancer.[30] Although presence of pre-existing HPV infection was not documented in every case, the oncogenic potential of this virus is well established. These findings reinforce the need for physicians to examine genital skin and to educate patients about HPV transmission and infection.

Prevention

Skin cancer prevention efforts are largely directed toward modifiable risk factors; UV radiation exposure is the most significant. Accordingly, the *American Cancer Society Goals and Objectives for 2015* aims to have 75% of people regularly using at least two sun-sensible measures, such as liberal use of sunscreen and wearing tightly woven clothing and hats.[3]

Patients must be educated about the importance of reducing intense UV exposure for themselves and their children. Routine well-child visits provide a forum to reach parents and their children before significant sun exposure occurs. Childhood sun exposure is a known risk factor for melanoma. By establishing preventative behavior patterns during the formative years, skin cancer can be prevented in current and potentially, future generations.

Although the value of sunscreen has been debated in the literature, regular use of sunscreen, especially in fair skinned individuals, is considered to be protective. As much as a 78% reduction in lifetime incidence of KCs has been proposed to result from regular use of sunscreen (SPF $\geq$ 15) during the first 18 years of life.[31] Even in older individuals with a history of significant exposure, regular sunscreen use can prevent development of new actinic keratoses and hasten resolution of old lesions. The protective effect of sunscreen on melanoma development is less clearly delineated. However, considerable evidence suggests that by blocking UV absorption and diminishing total UV exposure, sunscreen can prevent melanoma formation as well.

When addressing sunscreen, most dermatologists recommend products that provide both UVA and UVB protection with an SPF of at least 30. Patients must be instructed to reapply frequently (every 2-3 hours) and use this as part of a general sun protective approach. Sunscreens should not be used to lengthen time in the sun.

Frequent reminders about skin protection and detection practices are a critical component of this public health campaign; informed patients are more likely to use sun protection measures and to bring suspicious lesions to the attention of a physician.[32]

Conclusion

The public health impact of skin cancer is enormous and increasing. Sun-sensible measures need to be taught and encouraged for all ages. Early detection is essential to limit the morbidity and mortality associated with these tumors. The unique ability to visually detect these lesions enables the patient to take a more active role in early cancer detection by performing skin self-exams. Given the huge number of people affected, it is essential for primary care clinicians to be active participants in patient education and skin cancer detection.

Resources

The American Cancer Society (www.cancer.org, 1-800-ACS-2345), the American Academy of Dermatology (www.aad.org), and The Skin Cancer Foundation (www.skincancer.org, 1-800-SKIN-490) are national organizations with information on skin cancer available for physicians and the general public. Locally, there is a Mole Mapping Program, designed for early detection of melanoma in high-risk individuals, at the Pigmented Lesion Unit (444-7959) located at the Rhode Island Hospital campus, as well as a Multidisciplinary Melanoma Program (444-8852) designed for patients who are newly diagnosed with melanoma.

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Images in Medicine

Edited by John Pezzullo, MD

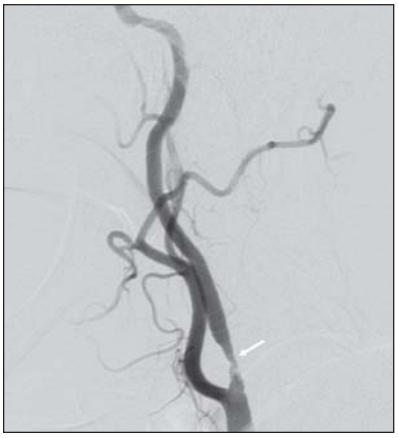

Figure 1a.

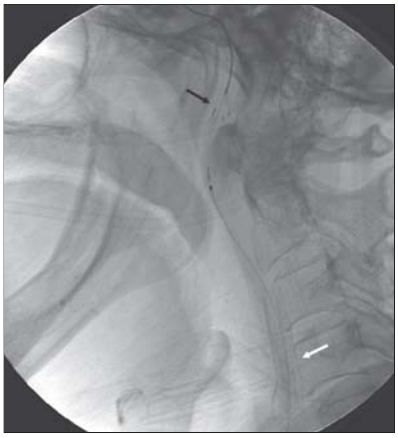

Figure 1b.

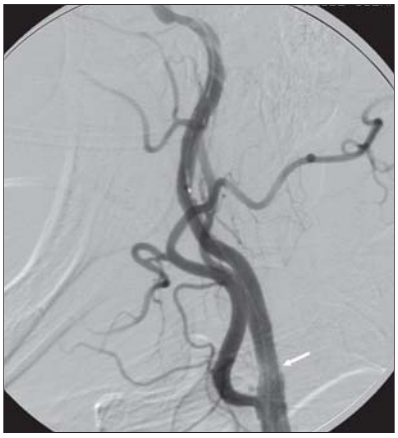

Figure 1c.

Carotid Artery Stenting using Distal Embolic Protection Device

A 64-year-old female with a right pulmonary mass (1.2cm) for planned surgical resection was noted to have a left carotid bruit on physical exam. Ultrasound and MRI exams showed 90% stenosis of the left **internal carotid artery (ICA)** origin and less than 50% stenosis of the right ICA. The patient was asymptomatic from a carotid standpoint. She was considered a high surgical risk for **carotid endartectomy (CEA)** due to a history of previous thyroid and cardiac surgery. Following consultation with Interventional Radiology the decision was made to pursue percutaneous left carotid treatment prior to lung surgery.

Carotid angiography confirmed high-grade stenosis of the left ICA (1a). The stenosis was crossed and the Accunet™ embolic protection device (Guidant Corp., Indianapolis, IN) was deployed above the stenosis to minimize risk of cerebral embolization (1b black arrow). An Acculink™ stent (Guidant Corp, Indianapolis, IN) was then deployed across the stenosis and dilated. (1b white arrow) Post deployment arteriogram confirmed no significant residual stenosis (1c). No significant complications occurred post procedure and the patient was discharged home on Plavix and ASA.

Discussion

Percutaneous treatment of carotid artery stenosis was first described in 1980.[1] Advances in stent design and the addition of Embolic protection devices have made the procedure safer. **Carotid Artery Stenting (CAS)** now represents an alternative to CEA, especially for high-risk patients. The worldwide technical success rate of CAS is 98.4 %.[2] The thirty-day minor /major stoke rates are 2.72% /1.49%, 30-day mortality rate is 0.86% and six and 12-month restenosis rates are 1.99% and 3.46%.[2]

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HOSPITALIZATIONS FOR AMBULATORY CARE SENSITIVE CONDITIONS

KAREN A. WILLIAMS, MPH, AND JAY S. BUECHNER, PHD

Hospital inpatient care is utilized to treat the most severe conditions of disease, illness and injury. With appropriate ambulatory care, some hospitalizations for certain conditions, called **ambulatory care sensitive conditions (ACSCs)**, are believed to be avoidable. Taken together, ACSC hospitalizations were estimated to account for 3.1 million hospitalizations nationwide, representing 12% of all hospitalizations in 1990.[1] Selected results from an analysis of the burden of ACSC hospitalizations in Rhode Island are presented here.

METHODS

Acute-care hospitals in Rhode Island have been reporting patient-level data for every patient discharged since October 1, 1989, as required by licensure regulations. The data items reported for each patient include demographics and clinical data coded to the **International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)**.[2]

Consistent with reports produced by the state of Massachusetts based on conditions originally compiled by Billings, this analysis examined discharges with any of 24 conditions defined as ACSC.[3, 4, 5] (Table 1) Specific definitions of the ACSCs are available upon request.

Hospitalizations for ACSCs cannot be avoided in all instances. The extent to which these hospitalizations are preventable varies by condition, general health status and other factors. In this analysis, "self-pay" as the expected source of payment was used as a proxy for uninsured. This analysis is limited to Rhode Island residents discharged from Rhode Island hospitals during 2001- 2003, excluding newborn infants.

RESULTS

On average, more than 19,000 ACSC hospitalizations occur each year, representing 17% of all discharges among Rhode Island residents and accounting for 12% of the total billed charges for inpatient care. (Table 2) Of the 57,749 ACSC discharges during 2001-03, 1,839 (3.2%) were uninsured.

ACSC discharges as a percent of total discharges increased with age, with the exception of the 0-17 years age group, whose proportion was almost as great as in the oldest age group. (Table 2) For the two extreme age groups, almost one quarter of all hospitalization are for ACSCs.

The percent of ACSC hospitalizations for patients without insurance was greater than for patients with insurance for all age groups. The difference between the two populations decreased with age and ranged from 8.8 percentage points among those ages 18 – 34 to 1.3 percentage points for those age 65 and older. (Figure 1) For all ages combined, the percentage of ACSC discharges was greater for the insured than the uninsured; this anomaly is due to the different age distributions of the insured and uninsured populations.

The most common specific ACSCs among discharges during 2001-2003 varied by age, with congestive heart failure, bacterial pneumonia and chronic obstructive pulmonary diseases ranked highest overall and together accounting for over half (55%) of all ACSCs. (Table 3) Bacterial pneumonia was a leading condition for all age groups, while asthma ranked highest among the younger age groups only. The most common ACSCs also varied by insurance status. Most notably, diabetes, celluli-

Table 1.
Ambulatory Care Sensitive Conditions (ACSCs)

Medical Condition
Angina
Asthma
Bacterial pneumonia
Cellulitis
Chronic obstructive pulmonary disease
Congenital syphilis
Congestive heart failure
Convulsions
Dehydration
Diabetes
Failure to thrive
Gastroenteritis
Grand mal status and other epileptic convulsions
Hypertension
Hypoglycemia
Immunization related and preventable conditions
Invasive cervical cancer
Iron deficiency anemia
Kidney/urinary infection
Nutritional deficiencies
Other tuberculosis
Pelvic inflammatory disease
Pulmonary tuberculosis
Severe ear, nose and throat infections

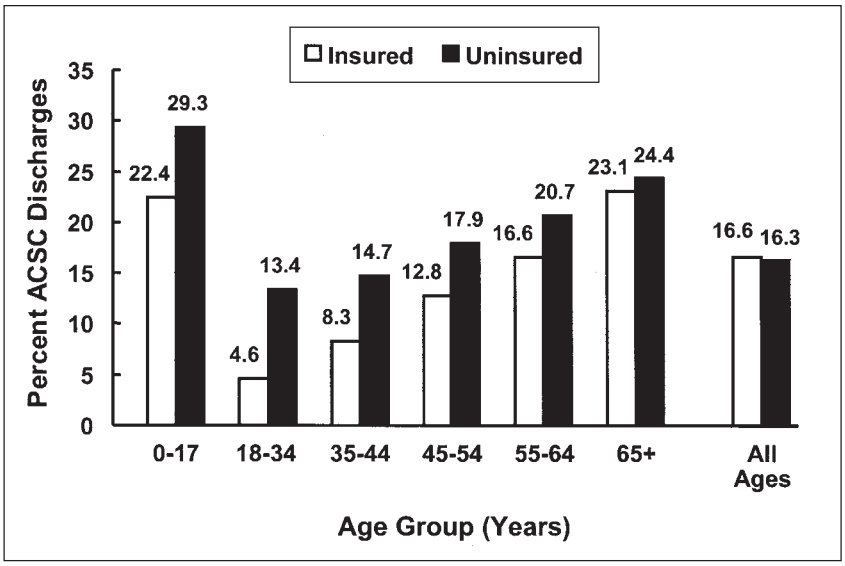

FIGURE 1. DISCHARGES FOR AMBULATORY CARE SENSITIVE CONDITIONS AS PERCENT OF ALL DISCHARGES, BY AGE GROUP AND INSURANCE STATUS, RHODE ISLAND RESIDENTS, 2001 – 2003.

Table 2.
Total Discharges, Ambulatory Care Sensitive Conditions (ACSC) Discharges and ACSC Discharges as Percent of Total Discharges, by Age Group, Rhode Island Residents, 2001- 2003

Age Group	Number of Total Discharges	Number of ACSC Discharges	Percent ACSC of Total Discharges
0 - 17 Years	24,976	5,627	22.53%
18 - 34 Years	58,616	3,084	5.26%
35 - 44 Years	40,356	3,513	8.71%
45 - 54 Years	38,185	5,012	13.13%
55 - 64 Years	37,188	6,237	16.77%
65 Years & Older	148,419	34,274	23.09%
All Patients	347,761	57,749	16.61%

Table 3.
Leading Ambulatory Care Sensitive Conditions by Age Group, Rhode Island Residents, 2001 – 2003

Age Group	Rank 1	Rank 2	Rank 3
0 - 17 Years	Asthma	Dehydration	Bacterial Pneumonia
18 - 34 Years	Asthma	Diabetes	Kidney/UTI
35 - 44 Years	Bacterial Pneumonia	Cellulitis	Asthma
45 - 54 Years	Bacterial Pneumonia	Chronic Obstructive Pulmonary Diseases	Cellulitis
55 - 64 Years	Chronic Obstructive Pulmonary Diseases	Congestive Heart Failure	Bacterial Pneumonia
65 Years & Older	Congestive Heart Failure	Bacterial Pneumonia	Chronic Obstructive Pulmonary Diseases
All Patients	Congestive Heart Failure	Bacterial Pneumonia	Chronic Obstructive Pulmonary Diseases

tis and asthma were leading conditions for the uninsured population overall, but ranked much lower for the insured population.

DISCUSSION

Hospitalizations for ACSCs comprise a large proportion of all inpatient care in Rhode Island, both among the insured and uninsured populations, and they account for an even greater proportion among those who are young and uninsured. The most commonly occurring specific ACSCs are different for patients of different age groups and for patients with and without health care coverage.

The rate of hospitalizations for ACSCs has been suggested as an indicator of the access to and the quality of the ambulatory care system serving the populations from which these inpatient discharges are drawn.[1] On that basis, this analysis demonstrates that many of the uninsured may lack access to high quality ambulatory care. Further analysis, e.g., by geographic area, by specific type of health care coverage, by socioeconomic status, by gender, by race and ethnicity, etc., may help identify other specific populations in Rhode Island with less than optimal ambulatory care.

Additionally, the overall volume of hospitalizations for ACSCs represents, in whole or part, a potentially avoidable burden on the state's health care system. Eliminating even a portion of these hospitalizations could free substantial resources for other health care services or even reduce the costs of health care coverage to employers, governments, and individual subscribers. These benefits would accrue in addition to the health benefits to those whose medical conditions were treated or controlled before progressing to a level of severity requiring hospital inpatient care.

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Advances in Pharmacology

Can Robitussin® DM Be Used To Treat Cough During Pregnancy?

Kristina E. Ward, PharmD

During cough and cold season, the question of whether Robitussin® DM is safe for use during pregnancy often arises. Robitussin® DM is available generically and contains guaifenesin (100 mg/5 mL) and dextromethorphan (10 mg/5 mL). Because both dextromethorphan and guaifenesin were marketed prior to the requirement for pregnancy information in labeling, a pregnancy category was not assigned to either ingredient; however, there is information available in the literature about the use of the individual ingredients during pregnancy.

Dextromethorphan

Dextromethorphan is the antitussive component of the combination and is a derivative of morphinan, a structural analog of codeine.[1,2] Use of the *d*-isomer avoids the addictive and analgesic properties present in the *l*-isomer and other codeine derivatives. Compared with codeine, the antitussive potency of dextromethorphan is nearly similar.[3,4] Dextromethorphan acts centrally in the medulla oblongata to raise the cough threshold and is also known to act as an antagonist at **N-methyl-D-aspartate** (**NMDA**) receptors; however, it is unclear whether its NMDA activity contributes to the antitussive effect since codeine does not bind to NMDA receptors.[1,5] Dextromethorphan is rapidly absorbed from the gastrointestinal (GI) tract with onset of cough suppression within 15 to 30 minutes and duration of effect between five to six hours.[1,2] Metabolism occurs in the liver via cytochrome P450 2D6 forming two inactive metabolites and one active metabolite. Cytochrome P450 2D6 activity may be increased during pregnancy potentially causing alterations in clearance of medications metabolized through this pathway, including dextromethorphan.[6]

A controversial animal reproduction study injected dextromethorphan into chick embryos consecutively for three days.[7] At the highest dose, increases in congenital anomalies (e.g., spinal and craniofacial defects) were observed. However, the findings were heavily criticized. The findings were not replicated in rats or rabbits at doses up to 100 times the human therapeutic dose.[8] Dextromethorphan has a molecular weight of 271 daltons which is small enough to be transferred to the fetus.[9] However, data from two surveillance studies of women who had taken dextromethorphan during the first trimester, one being the Collaborative Perinatal Project, found no relationship between the use of dextromethorphan and the incidence of congenital malformations.[10,11] Additionally, two recent case-control studies also found no evidence of increased risk of congenital malformations with dextromethorphan use during the first trimester.[12,13]

Guaifenesin

Guaifenesin is an expectorant with no antitussive effect. Although guaifenesin's mechanism of action is not completely known, it increases the volume and decreases the viscosity of respiratory tract secretions. [14,15] Guaifenesin is well-absorbed from the GI tract with approximately 60% of guaifenesin hydrolyzed in the blood.[14]

Peer-reviewed evidence supporting the effectiveness of guaifenesin as an expectorant is limited.[15] One study evaluating the effectiveness of guaifenesin in patients with bronchitis found it ineffective.[16] A second study in patients with colds found that guaifenesin subjectively thinned mucus; however, the guaifenesin treatment dose was two times the recommended dose.[17]

Table 1. Dextromethorphan-Only Cough Suppressants

Brand Name	Dosage Form	Strength
Delsym®	Suspension,	30 mg/5 mL extended release
Hold® DM	Lozenge	5 mg/lozenge
Robitussin® Cough Calmers	Lozenge	5 mg/lozenge

Guaifenesin has a molecular weight of 198 daltons, indicating possible placental transfer. Data from three surveillance studies regarding the use of guaifenesin during the first trimester is available.[9-11] An increase in the risk of inguinal hernias was noted with the first trimester use of guaifenesin in 197 mother-child pairs during the Collaborative Perinatal Project.[4] However, when analyzed for guaifenesin exposure anytime during pregnancy this association was not significant. Two other surveillance studies assessing 241 and 141 newborns whose mothers ingested guaifenesin during the first trimester found no associations between guaifenesin use and congenital defects.[9,11]

Conclusion

The use of dextromethorphan for cough during pregnancy does not appear to produce an increased risk of congenital malformations in newborns. Similar data with guaifenesin also suggests it is safe to use during pregnancy. However, in general, the use of drugs should be minimized whenever possible during pregnancy. Because the efficacy data supporting the use of guaifenesin as an expectorant is scant, the use of a dextromethorphan-only cough suppressant (see Table 1) should be considered. Additionally, patients should be advised to avoid cough preparations that contain alcohol.

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PUBLIC HEALTH BRIEFING
RHODE ISLAND DEPARTMENT OF HEALTH
DAVID GIFFORD, MD, ACTING DIRECTOR OF HEALTH
EDITED BY JOHN P. FULTON, PHD

THE RHODE ISLAND SMOKEFREE PUBLIC PLACE AND WORKPLACE LAW: ESTIMATED IMPACT ON ASTHMA IN THE RHODE ISLAND WORKFORCE

COLLEEN CARON, PHD, ANNIE GJELSVIK, PHD, ELIZABETH HARVEY, MA, MS

Two distinguishing features set health legislation apart from other public health interventions. First, health legislation has far reaching effects on population health by impacting large societal segments. Second, its impact is sustained for the life of the legislation. In contrast, one-on-one health interventions or small-scale health campaigns marked by definitive start and end points risk message loss within a message-inundated society.

Under recently enacted Rhode Island state law, workplaces are now smoke-free environments (Public Health & Safety Act of 2004 - Smokefree Public Place and Workplace Law, Chapter 23-20.10).[1] With few exceptions, employees are guaranteed a workplace environment free of the prolonged and harmful effects of **second-hand smoke (SHS)** exposure. The adverse effects of SHS include respiratory effects such as asthma, emphysema, and lung cancer, and cardiovascular effects such as heart attack and stroke. Seven states have enacted smoke-free workplace or public place smoke-free laws.[2]

SHS is known to trigger asthma symptoms, and is also clearly implicated in the initial development of asthma.[3] Research demonstrates that 8% of adult-onset asthma (asthma diagnosed at ages 18 and above) is attributed to SHS.[4] SHS workplace legislation has a dual public health benefit specific to individuals with asthma. First, it reduces the risk of asthma exacerbations for employees with asthma, thus expanding employment opportunities for those with asthma. Second, it has the potential to reduce the development of adult-onset asthma, including work-induced adult-onset asthma. Estimating the magnitude of these two public health benefits is the focus of this paper.

Asthma is a leading chronic disease in the United States, affecting 11% of adults 18 and older (2002), [5] including an estimated 13% of Rhode Island adults ages 18-64 who report ever having had asthma (diagnosed by a medical provider, i.e., "lifetime asthma"). A smaller group, slightly more than 8% of Rhode Islanders ages 18-64 in 2002, report having asthma at the present time (diagnosed by a medical provider, i.e., "current asthma").[5]

Estimates of adult-onset asthma attributed to the workplace vary greatly. Some studies attribute 10 to 15% of adult-onset asthma cases to workplace exposures, while others place the estimate between 2 and 26%.[6,7] Work-related asthma is classified as one of two types, *work-aggravated* asthma and *new-onset* or *work-induced* asthma.[7] Work-aggravated asthma is defined as previously-diagnosed asthma with an exacerbation of symptoms after exposure to substances in the workplace.[7] *New-onset asthma* is defined as newly-diagnosed asthma developed after exposures to substances in the workplace. "Newly diagnosed" is defined as "never diagnosed with asthma" or "previously diagnosed and symptom free for two years."[7] SHS exposure in the workplace is a potential cause of both *work-aggravated* asthma and *new-onset* or *work-induced* asthma.[4]

METHODS

The public health impact of the "Public Health & Safety Act of 2004" was assessed using data from the Rhode Island Behavioral **Risk Factor Surveillance System (BRFSS)** collected in calendar year 2002 and from statistics published by the United States Department of Labor, Bureau of Labor Statistics, for the year 2002. The BRFSS conducts a national telephone survey of randomly selected non-institutionalized adults (ages 18 and older) who live in households with telephones, monitoring the prevalence of behavioral risk factors for leading causes of disease and death. The 2002 BRFSS survey contained sufficient asthma-related questions to estimate asthma prevalence among Rhode Island adults, ages 18-64, traditionally the group of focus for workforce statistics in the United States. Data from the United States Bureau of Labor statistics were used to determine the number of individuals in the Rhode Island workforce.

RESULTS

Lifetime Asthma

In 2002, a total of 468,451 persons were employed in Rhode Island private industry and government combined.[8] In the same year, an estimated 13% of employed Rhode Island adults ages 18-64 reported lifetime asthma in response to BRFSS survey questions.[5] Therefore, an estimated 60,900 adults employed in Rhode Island in 2002 had lifetime asthma. (468,451 employed persons times 13% of employed adults ages 18-64 with lifetime asthma equals 60,899.)

Employed adults with lifetime asthma include persons diagnosed at ages younger than 18, and persons diagnosed at ages 18 and above (adult-onset). In Rhode Island, 45% of adults with lifetime asthma reported adult-onset.[5] Therefore, an estimated 27,400 employed Rhode Island adults

with lifetime asthma experienced the onset of asthma as adults. (60,900 employed Rhode Island adults with lifetime asthma times 45% of adults with lifetime asthma who reported adult asthma onset equals 27,411.)

On the basis of previous studies, about 15% of adult-onset asthma may be work-related. Therefore, 4,100 adults employed in Rhode Island may have developed work-related, adult-onset asthma, a portion of which is attributable to SHS (15% of 27,411 employed Rhode Island adults with adult-onset lifetime asthma).

Current Asthma

Similar logic was used to compute estimates for adults with current asthma: An estimated 38,880 adults employed in Rhode Island had current asthma in 2002. Of these 38,880, an estimated 19,440 developed asthma as adults, and of these 19,440, about 2,916 may have asthma related to asthma triggers in the workplace, including SHS.

Discussion

Rhode Island's Smokefree Public Place and Workplace Law guarantees legal protection from exposure to SHS in the workplace, thus protecting about 60,900 adult workers with lifetime asthma and 38,880 adult workers with current asthma.

SHS is one of many factors contributing to work-related asthma.[7] Thus, although the new workplace law will undoubtedly prevent many new cases of work-related adult-onset asthma, it will not eliminate *all* new cases. Nonetheless, every case prevented will preserve quality of life and lower health care costs, because asthma leads to days missed from work, ER visits and hospitalizations.[9] To illustrate, consider recent asthma data from Rhode Island's hospital discharge data set. In 2002, about $6,420,000 was expended on adults hospitalized for asthma (642 hospitalizations at an average cost of $10,000 per hospitalization). With the new smoke-free workplace law taking effect, this cost, as well as other costs of asthma morbidity, will probably decline.[4]

This analysis contains limitations. First, the estimates are not adjusted for existing workplaces prohibiting smoking; these data are not available. Such corrections would most likely generate lower estimates than presented here. Nonetheless, such legislation brings legal protection to an otherwise voluntary effort. Second, the workforce data contain data on all workforce members regardless of age. Although the preponderance of workers in Rhode Island are in the 18-64 age group, like the asthma prevalence estimated presented in this analysis. Some are undoubtedly older and younger. However, the prevalence of asthma is higher in younger age groups and lower in 65 and older age groups.

The Public Health & Safety Act of 2004 landmark legislation legally protects an estimated 60,899 employed Rhode Island adults with lifetime asthma and an estimated 38,881 employed Rhode Island adults with current asthma against exposure to workplace SHS.

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A Physician's Lexicon

The Colorful Words of Medicine, part I

Accurate description, without excessive verbiage, is the hallmark of a competent physical examination record. The portrayal of a skin rash, for example, demands information concerning many of its physical characteristics, including color.

Describing color, to both diagnostician and pathologist, becomes a meaningful way of conveying a faithful description of the lesion under scrutiny. As with so many aspects of medical terminology, the two Classical languages - Greek and Latin - each contribute roots to define the known colors.

Yellow, for example: The Greek word for yellow is *xanthos,* as in xanthine, xanthoma and xanthochromia. Xanthippe's name—she was the ill-tempered wife of Socrates—literally means the yellow horse. Latin has many words for yellow, one being *galbinus.* This word has evolved into the French word, *jaune,* the precursor of the English, jaundice. *Flavus* is yet another Latin term for yellow, as in such words as flavobacteria, riboflavin and flavicid. And *luteus,* as in corpus luteus, is a further Latin word for yellow.

The Greek root for black [*melano-*] appears in such terms as melancholy, melanoma, melena and Melanesia. The Latin for black, *nigrum* or *niger*, is found in such words as nigritude, denigrate, substantia nigra and nigricans. The Latin word, *fuscus*, means brownish-black and gives rise to such English words as obfuscate [to make dark, to confuse]. It is distantly related to the English word, furtive, [concealed, darkened, stealthy.]

The Greek word for white, *leukos*, is the etymologic root for leucocyte, leukemia and leukoderma. And the Latin words for white [*albus* and *candidas*] form the basis for albino, album, albumen, candid, candidate [because Roman candidates for office wore white togas], candle, incandescent and Candida. The Latin, *pallidus*, suggesting paleness more than whiteness, appears in such words as pallor and globus pallidus. Palliation, to relieve by soothing rather than curing, on the other hand, is derived from the Latin, *palliatus*, meaning to cloak.

The Greek root for grey is *polios*, as in poliosis and poliomyelitis. Its Latin counterpart is *griseus*, as in griseofulvin, grizzly and ambergris.

Words derived from the Greek and Latin terms for yet other colors will be considered in next month's column.

– Stanley M. Aronson, MD, MPH

Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Vital Statistics

Edited by Roberta A. Chevoya

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	March 2004	12 Months Ending with March 2004		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	245	3,031	283.3	4,416.5
Malignant Neoplasms	222	2,429	227.1	7,406.0
Cerebrovascular Diseases	44	533	49.8	850.0
Injuries (Accident/Suicide/Homicide)	42	476	44.5	7,412.0
COPD	58	510	47.7	412.5

Vital Events	Reporting Period		
	September 2004	12 Months Ending with September 2004	
	Number	Number	Rates
Live Births	993	14,005	13.1*
Deaths	706	10,077	9.4*
Infant Deaths	(6)	(77)	5.5#
Neonatal deaths	(2)	(61)	4.4#
Marriages	1052	8,277	7.7*
Divorces	257	3,205	3.0*
Induced Terminations	430	5,502	392.9#
Spontaneous Fetal Deaths	76	1,235	88.2#
Under 20 weeks gestation	(70)	(1,164)	83.1#
20+ weeks gestation	(6)	(71)	5.1#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,069,725

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population # Rates per 1,000 live births

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Ninety Years Ago, March 1915

An editorial urged members to contribute "works of fiction which they have read and for which they have no further use" to the newly-established Patients' Library at Rhode Island Hospital. "The tedious days of convalescence are a source of anxiety to the physician, to the nurse and to the hospital authorities, and anything which will tend to help pass away the time during the interval of serious illness and discharge from the hospital will be of decided service."

A second editorial urged members to obey the Harrison Law, effective March 1, 1915. The law required physicians who dispensed their own drugs to use blank forms from the Commission of the Internal Revenue to order supplies, to keep a record of all preparations with opium or coca leaves, and to keep an inventory of those substances in their possession. "However much we may disagree with its necessity or find fault with the provisions of this law, we must obey it."

F.T. Rogers, MD, in "A Study of the Workmen's Compensation Act as it Affects Rhode Island Physicians," reported on a survey of 500 practicing RI physicians: 230 responded. Only 92 reported any problem with payment; 104 reported no change in income; 58 reported an increase; 68, a decrease. The author noted, "The testimony of the profession is almost unanimous that the difficulties arising from the enforcement of the act are due, not to the employer, but to the insurance companies, who, in spite of their great increase in premiums, endeavor to further augment their dividends."

Roland Hammond, MD, in "The Use of the Autogenous Bone Graft," reported on two cases. One patient had had osteomyelitis of the tibia; the second had an "ununited" fracture of the tibia.

Fifty Years Ago, March 1955

Alex Burgess, Sr,, MD, Commissioner, Joint Commission on Accreditation of Hospitals, contributed "What Makes a Good Hospital?" His response: "good people," not bricks and mortar.

Bert S. Jeremiah, MD, in "Recent Advances in the Management of Severe and Extensive Burns," recommended autoclaved gauze or rayon strips impregnated with furacin or Vaseline for immediate covering, then for treatment, closed pressure dressings.

Joseph C. O'Connell, MD, in "Extending Voluntary Medical Care Coverage in Rhode Island," noted that the Physicians Sevice Program had enrolled 442,777 Rhode Islanders after five years of operation. Almost all (871) physicians in the state participated.

Twenty-Five Years Ago, March 1980

In "Dean's Message," Stanley M. Aronson, MD, described "A New Approach to CME." The medical school invited practicing physicians to participate, as observer-students, in one of the brief, intensive second-year courses (e.g., cardiology, nutrition, nephrology, parasitology).

Guy A. Settipane, MD, in "Aspirin Intolerance Presenting as Chronic Rhinitis," discussed the case of a 52 year-old woman. The author cautioned that "Aspirin intolerance should be considered in the diagnosis of unexplained rhinitis, nasal polyps and eosinophilia."

Siegfried M. Pueschel, MD, Richard E. Frates, MD, and Don B. Singer, MD, discussed "Small, Post-Dates Infant with Severe Respiratory Distress" in part of a Clinical Pathological Conference, in the Section of Pathology.

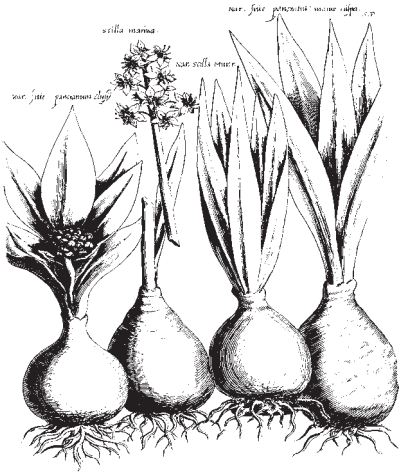
W. Martin DeLuca, PA, Clarence H. Soderberg, Jr, MD, Raymon S. Riley, MD, Patricia A. O'Shea, MD, and Gayle S. Griffiths, PA, contributed "Solitary Rhabdomyosarcoma of the Pericardium: A Case Report and Pathologic Discussion." A rare tumor was found to be the cause of unexplained congestive failure.

FORTHCOMING

Medicine & Health/Rhode Island
April 2005

Hospice

Guest Editor:
Stanley M. Aronson, MD, MPH



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What's in a Name???

GOOD - authentic, honest, just, kind, pleasant, skillful, valid

NEIGHBOR - friend, near

ALLIANCE - affiliation, association, marriage, relationship

CORPORATION - company, business establishment

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