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## COMMENTARIES



## CONTRIBUTIONS

***Special Issue:*** **ONCOLOGY**
***Guest Editor:*** **Jorge J. Castillo, MD**



## COLUMNS



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# Commentaries

## Localizing the Wandering Uterus

**Conversion disorders have been recog-**nized forever although not formally studied until the great French neurologist, Charcot, focused his attention on this problem in the mid 19th century. The patients were predominantly women, perhaps all women, who manifested a variety of clinical signs that could not be explained by any known derangements of neurological structures. Freud, who studied with Charcot, developed an interest in this area, later publishing the famous case of conversion-weakness in Anna O. Anna O, of course, was cured by psychoanalysis and then went on to a prominent career as a social worker.

The term "conversion disorder," which has been used interchangeably with "hysteria," refers to the presumed mechanism by which non-organically explicable neurological abnormalities result when emotional distress is allegedly "converted" into physical manifestations. The term "hysteria," which predated Charcot, is derived from the Greek term for uterus. It was used to describe these disorders because they were thought to occur only in women, and were ascribed to a problem with the uterus, which was thought to wander.

Conversion symptoms are so common that they are discussed in the vernacular in such phrases as, "so-and-so is a pain in the neck," (or some other place). What this phrase means, of course, is that "so and so" causes so much aggravation that one experiences his presence as physically painful. It is common to blame headaches, for example, on stress at work, difficulty with relatives, etc. It is unlikely that anyone doubts that stress may cause pain in vulnerable people. Yet the notion that stress may cause weakness, numbness, blindness, muteness, tremors, impaired walking, or seizures, is accepted more in the general sense than in a specific case. "Yes, I think that stress may cause these problems in some people, but not in me."

A few decades ago, before the era of modern imaging and invasive testing, several studies reviewed the long-term outcome of patients who had been diagnosed with psychogenic explanations for their symptoms and signs. A large percentage, varying from 30-50%, ultimately *were* explained as the result of organic lesions. Neurological patients were found to have MS or unusual, but clearly organic, forms of epilepsy. Inflammatory bowel disease explained many with non-specific GI symptoms. Systemic lupus erythematosis and other autoimmune disorders became apparent. Metabolic derangements became identifiable, and these, in retrospect, explained the earlier symptoms. This undermined everyone's confidence in their diagnoses, particularly psychiatrists who were put in the difficult position of trying to "cure" someone of a presumed psychogenic disorder that later turned out to be multiple sclerosis or a brain tumor. However, in recent times, similar studies have revealed an amazingly low incidence of mis-diagnoses. The vast majority of current diagnoses of non-organic disorders are, it seems, correct. The problem thus moves from, "is it organic?" to "how did this happen?" and "what to do about it?" The answers are, unfortunately, not known. Psychoanalysis has been more helpful in explaining than in treating it.

As a movement-disorders specialist, I know most about conversion disorders in this area. The diagnosis of psychogenic disorder is made in about 5% of new patients referred to movement-disorder centers in the western world. This is a fairly substantial number and certainly underestimates the problem because many of the disorders are transient and resolve before the appointment to the specialist's office. My experience doing general neurology consults in hospitals suggests a percentage quite a bit greater than 5%. It is not terribly uncommon to give tPA, for example, to patients who were thought to have had strokes, but actually had psychogenic weakness. I've seen one patient who has had tPA twice for psychogenic "strokes."

The natural history of conversion disorders in general is interesting. The vast majority resolve without treatment in the first few weeks, while those that persist for several months generally persist forever. These are often disabling, and no treatment is known to be effective. The patients generally do poorly. The neurologist dismisses them with, "no neurological disorder" and then the psychiatrist dismisses them with "no psychiatric disorder." It is only in recent years that some neurologists have at least continued to follow these patients, even if the etiology of the disorder is psychiatric, just as we follow people with untreatable degenerative disorders. This is support and is important, but it is not treatment, at least not specific treatment.

While many of these patients share a variety of common psychiatric comorbidities, such as childhood abuse, personality disorders, post traumatic stress disorders, not all do, and many, on the surface, appear to not have much in the way of psychiatric dysfunction. This, of course, makes life hard for the psychiatrist and, worse for the poor patient.

In recent years, there have been studies trying to figure out "how" rather than "why" conversion disorders take place, by using fMRI, a crude measure of brain activity, while the patient has conversion symptoms, and comparing the results to normal controls feigning the same disorder. In one study however, the conversion patients had intermittent tremors and the fMRI were obtained while the patient had the conversion tremor and then again when the same patient voluntarily mimicked the tremor, thus acting as his own control. The fMRI patterns differed when the conversion disorder patients had their conversion-tremor, presumably voluntary but unconscious, from when they feigned the exact same tremor. This implies that there are physiological underpinnings to explain how some patients develop neurological symptoms which are generated unconsciously. These physiological alterations will not explain why some patients develop these problems but may, in time, suggest how to treat them. It is not clear in this early stage whether this imaging modality will allow us even to diagnose the problem.

These studies are important because conversion disorders are common, confounding to all involved and may provide insights into the dynamics of unconscious motivations. The different conversion symptoms have been associated with different brain alterations. No single region has been implicated to suggest that there is a region devoted to "self-awareness." The data thus provides a philosophical

conundrum. How can an unconscious disorder be "non-organic?"

– Joseph H. Friedman, MD

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Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001-2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.

# A Terrible Spirit Hath Taken Him

**How do we establish the identity, the individuality, of a** specific systemic disease? We gather its outward manifestations such as fever, weakness, rash or pain, then solemnly declare its separateness from other known diseases. Finally we confer a name upon it. Human progress, though, is glacially slow, measured more in millennia than in years; and of humanity's many worthy disciplines, none has progressed more slowly than rational medicine.

Consider our understanding of a family of illnesses called epilepsy. The signs that announce epilepsy emerge dramatically, are often sharply defined and so distinguishable from other systemic disorders as to separate epilepsy from the banal family of known diseases. Indeed, few diseases arise so abruptly and speak so audaciously. A fever, even a devastating fever, can be the sign of countless disorders, but a convulsion culminating with the loss of consciousness – a falling down – can only herald something perilously different.

And so, in the eyes of both ancient physicians and equally ancient non-medical observers, epilepsy - the Falling Sickness - was set apart and considered beyond the domain of conventional medicine since it was obviously a manifestation of spirit-possession.

The Bible tells this plaintive story: "And behold, a man of the company cried out, saying, Master, I beseech thee, look upon my son: for he is mine only child. And lo, a spirit taketh him, and he suddenly crieth out; and it teareth him that he foameth again, and bruising him hardly departeth from him. And I besought thy disciples to cast him out; and they could not." (Luke 9: 38 – 40.)

Seeing a child – or a young adult – suddenly and without visible provocation become transformed, consumed by convulsions, incontinent, crying in incomprehensible words as though talking in an alien language, bereft of consciousness – or sometimes transfigured to a state of exalted consciousness – this surely cannot be some mundane disorder much like a rheumatism or a belly ache. And by its impetuous appearance, it must certainly be an abrupt invasion from without.

By common consent, and common sense, epilepsy was defined as a problem to be confronted only by those skilled in challenging exotic spirits or demons and adept in their expulsion.

Spirit possession was the prevailing causation of epilepsy through the 19th Century. Romans, demonstrating an even-handed attitude, called the disease either *morbus sacer* (the sacred disease), *morbus demoniacus* (the demonic disease) or *morbus comitialus* (the public place disease) Yet even four centuries before Roman ascendancy, Hippocrates (c.460 - 370 BCE) denied an extracorporeal origin of epilepsy declaring, "Neither truly do I count it a worthy opinion to hold that the body of man is polluted by God, the most impure by the most holy." Epilepsy, he concluded, is no different that other diseases.

A final comment by Hippocrates: He declared that epilepsy can be cured ". . . without minding purifications, spells and all other illiberal practices of a like kind." Galen, some five centuries later, agreed that epilepsy was surely in the realm of the secular, treatable diseases, although he incorrectly ascribed epilepsy to his theory of humors.

Yet these classical voices of antiquity, while heard, were not heeded. The satanic origin of epilepsy was an unqualified axiom for another millennium. (See, for example, the Salem witch trials of 1692.)

John of Gaddesden (1280 – 1361), court physician to King Edward I and England's most prominent physician of his age, described how to distinguish satanic possession from mundane epilepsy: "Utter these words into the ear of the suspect: 'Depart demon and go forth.' If he be lunatic or demoniac he immediately becomes dead for nearly an hour. If he does not fall when he hears this word, then you know he is epileptic."

Demons were still alive and thriving as etiologic agents in the late 17th Century. Thomas Willis (1621 – 1675), with neither irony nor tongue in cheek, declared: "As often as the Devil is permitted to afflict Miserable Mortals with his delusions, he is not able to draw more cruel arrows . . . than by the assaults of this Monstrous Disease."

And to prove the ubiquity of the Devil even in artless, guileless children, the great Dutch physician Gerhard van Swieten (1700 – 1772) wrote: "I have seen an innocent boy of four years of age, who, as soon as he began to repeat the Lord's prayer, was immediately convulsed." A credulous younger van Swieten was certain of the tangible reality of demonic possession. But latter in life, as court physician to Empress Maria Theresa, he decried this superstition that had infiltrated medicine; and it was Swieten who later denounced the beliefs, widespread in Austro-Hungary, in vampirism and other demonic persuasions.

– Stanley M. Aronson, MD

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# Non-AIDS Defining Cancers

*Jodi L. Layton, MD, and Jorge J. Castillo, MD*

**Reductions in HIV-associated morbidity** and mortality in the era of **highly active antiretroviral therapy (HAART)** have been accompanied by increases in the incidence of some malignancies in people with HIV/AIDS. Indeed, malignancy is now one of the most frequent causes of death and leading cause of hospitalizations in HIV-infected people in the HAART era.[1] The **World Health Organization (WHO)** recognizes three malignancies as AIDS-defining cancers: **Kaposi sarcoma (KS), non-Hodgkin Lymphoma (NHL),** and cervical cancer. These neoplasms were called "AIDS-defining" because of their incidence in patients with low CD4 counts; hence, they are thought to be directly related to the degree of immunodeficiency.

In the last decades, in people with HIV/AIDS, **non-AIDS-defining cancers (NADC)** (anal cancer, liver cancer, skin cancer, Hodgkin lymphoma, head and neck cancer, lung cancer, among others) have been increasing. These neoplasms occur with greater frequency in HIV-positive patients than in the general population, but are not thought to be directly associated with the degree of immunosuppression. Some of these malignancies are associated with risk factors thought to be more common in HIV-positive populations (smoking, alcohol consumption and coinfection with oncoviruses), but for others the underlying pathophysiology is less understood.

## Epidemiology of NADCs

Studying the epidemiology of malignancies in the pre- and post-HAART eras has proven challenging because most data do not correlate CD4 counts at the time of malignancy diagnosis or during the course of treatment for specific cancers. However, the overall trend has been that incidence of NADCs has increased in excess of what would be expected in a comparable non-HIV infected population.[2,3] A tool for better understanding this phenomenon is the **standardized incidence ratio (SIR)**.

SIRs measure the incident number of cases in an HIV-positive population as compared to what the incidence in this population would be expected to be if all individuals in the population were HIV-negative. Using the example of AIDS-defining cancers, the overall risk of KS and NHL have decreased in the era of HAART, but they still occur much more commonly than would be expected if the members of the population were not infected with HIV. The SIR for KS, NHL and cervical cancer are as high as 3640, 350 and 22, respectively. A recent report shows that the SIR for all NADC in the HAART era is 2.5 while in the pre-HAART era was 0.95.[3] However, the SIRs vary depending on the malignancy;' for example, the SIR for anal cancer have increased to 141 while the SIR for prostate cancer has not increased. The incidence of NADCs and AIDS-defining cancers in Rhode Island from 2004 to 2008 are shown in Table 1.

## Clinical Presentation

Overall, HIV positive patients with NADCs present with more advanced disease with overall worse prognosis compared to their HIV negative counterparts. This is true even for malignancies with the same incidence rates in HIV positive and negative populations. The reasons for these differences are not well understood, but likely vary depending on the malignancy and relevant risk factors. Additionally, the overall poorer health of patients with HIV, the greater number of comorbidities in HIV-positive patients, and the presence of other co-infections such as HCV, HPV, and HHV8 may play a role in the presentation and aggressiveness of NADCs.

## Lung Cancer

Although the SIR is only between 2 and 4, lung cancer is the most frequent NADC in the HAART era because lung cancer is common in both HIV-positive and negative populations.[4]. Adenocarcinoma is the most common histological subtype seen in HIV/AIDS patients. The higher than expected incidence is likely not directly related to HIV status, but is more likely related to the high prevalence

**Table 1.** Number of cases of AIDS-defining and non-AIDS-defining cancers in Rhode Island and The Miriam Hospitals from January 2004 to December 2008 (AIDS patients only)

| | Rhode Island Hospital | The Miriam Hospital | Number of cases (percentage) |
|---|---|---|---|
| **AIDS-defining cancers** | | | |
| Non-Hodgkin lymphoma | 11 | 24 | 35 (25%) |
| Kaposi sarcoma | 8 | 17 | 25 (18%) |
| Cervical cancer | 1 | 1 | 2 (1%) |
| **Subtotal** | **20** | **42** | **62 (45%)** |
| **Non-AIDS-defining cancers** | | | |
| Hodgkin lymphoma | 3 | 6 | 9 (7%) |
| Head & neck cancer | 5 | 5 | 10 (7%) |
| Liver cancer | 1 | 7 | 8 (6%) |
| Lung cancer | 2 | 5 | 7 (5%) |
| Anal cancer | 0 | 5 | 5 (4%) |
| Gastrointestinal cancers* | 2 | 9 | 11 (8%) |
| Genitourinary cancers** | 3 | 6 | 9 (7%) |
| Leukemias | 2 | 3 | 5 (4%) |
| Other solid malignancies | 5 | 7 | 12 (9%) |
| **Subtotal** | **23** | **53** | **76 (55%)** |
| **Total** | **43** | **95** | **138 (100%)** |

*Includes esophageal, gastric, pancreatic and colorectal cancers

**Includes renal, prostate, bladder and testicular cancers

of tobacco use in the HIV population. Current recommendations are to stage and treat patients without regard to HIV status.

### Hodgkin Lymphoma

HL is another common NADC. HIV-positive patients typically present at more advanced stages relative to their HIV-negative counterparts and extranodal involvement is common.[5] HL in HIV-positive patients tends to be histologically and clinically more aggressive. Of note, almost all cases of HL in HIV patients are EBV positive. There is an increased risk of HL at CD4 counts between 150-275 cells/mm$^3$, suggesting that the pathophysiology of the disease is modulated by moderate immunosuppression or immune reconstitution.[6] However, HL occurs less frequently at CD4 counts of less than 150 cells/mm$^3$; hence, one can infer the exact mechanism is not immunosuppression alone. The general treatment approach is initiation of HAART plus chemotherapy (ABVD). The data on radiation therapy in HIV-associated Hodgkin lymphoma are limited.

### Head and Neck

The increased incidence of head and neck cancers in HIV-positive patients may be due to a number of factors including tobacco use and co-infection with HPV (particularly in men who have sex with men). Patients present at younger ages and with more advanced disease when compared to their HIV-negative counterparts.[7] Head and neck cancers associated with HPV have a better overall prognosis than those associated with tobacco use. Treatment options are the same as for HIV-negative patients and focus on loco-regional control with surgery and radiation therapy or systemic therapy for metastatic disease. Notably, HIV-positive patients experience more severe and frequent side effects from therapy, which may ultimately prevent or inhibit aggressive approaches. HIV-positive patients often experience more severe xerostomia, oral infections, severe mucositis and secondary significant malnutrition. Clinicians must closely weigh the overall performance status of HIV-positive patients when deciding treatment options of head and neck cancers.

### Hepatocellular Carcinoma

Because hepatitis C and HIV have similar routes of transmission, HIV- positive patients are at an increased risk to develop **hepatocellular carcinoma** (HCC). Approximately 30% of HIV-positive patients are co-infected with hepatitis C.[8] The relative efficiency of transmission of both viruses differs by route; thus the co-infection rate varies significantly by risk group: IV drug users have the highest incidence of co-infection while heterosexual partners the least. Additionally, increased rates of alcohol consumption in the HIV-positive population and higher rates of liver disease may also increase the risk for HCC. As with all forms of HCC, treatment options remain limited. Liver transplant may be considered in some patients, but the efficacy of this in an immunosuppressed high-risk population remains unknown.

**Overall, HIV positive patients with NADCs present with more advanced disease with overall worse prognosis compared to their HIV negative counterparts.**

### Anal Cancer

**Human papilloma virus** (HPV), another co-infector with HIV, is a risk factor for invasive epithelial dysplasia and anal cancer. As such, there is a significantly increased risk of anal cancer in HIV-positive populations, particularly in patients who practice anal-receptive sex.[9] It is unclear if HAART has affected the incidence of this malignancy. Treatment is the same for patients with and without HIV infection. The reported increase incidence may represent a true increase likely secondary to HAART therapy or may represent increased detection with improved screening with anal PAP smears and more frequent clinical evaluations. Routine anal screening for HIV-positive patients who practice anal intercourse is recommended; however, anal cancer can occur in the absence of anal intercourse. The role of HPV vaccines in the prevention of anal cancer in HIV-positive patients remains unknown.

### Breast Cancer

Breast cancer occurs at approximately the same incidence in HIV-positive patients as compared to HIV-negative patients. However, when breast cancer occurs in HIV-positive patients, the malignancy tends to be bilateral and poorly differentiated with the early development of metastases.[10] Some researchers speculate the progressive disease may be

**Table 2.** Standardized Incidence Ratios (SIR) of selected non-AIDS defining cancers from recent large-scale studies* (post-HAART era)

| Non-AIDS defining cancer (NADC) | Engels (2006) | Long (2008) | Dal Maso (2009) | Powles (2009) |
|---|---|---|---|---|
| Anal cancer | 19.6 | 39 | 44 | 141 |
| Liver cancer | 3.3 | 16.5 | 6.4 | 7 |
| Head/neck cancer | 2.1 | 5.1 | 1.8 | 1.5 |
| Lung cancer | 2.6 | 5.5 | 10.3 | 1.5 |
| Melanoma | 1 | 4 | 0.6 | 2.7 |
| Skin cancer (non-melanoma) | NR | NR | 1.8 | NR |
| Prostate cancer | 0.5 | 0.6 | NR | 0.9 |
| Kidney cancer | 1.9 | 2.9 | 0.7 | NR |
| Penile cancer | 8 | 24.2 | 12 | NR |
| Vulvar/vaginal cancer | 4.4 | NR | 24.3 | NR |
| Brain cancer | 0.5 | NR | 3.2 | 1.6 |
| Colon cancer | 1 | 0.5 | 1.4 | NR |
| Breast cancer | 0.8 | 0.6 | 0.6 | NR |
| Hodgkin lymphoma | 13.6 | 9.8 | 20.7 | 32 |
| Multiple myeloma | 2.2 | 3 | 3.9 | NR |
| **All NADC** | **1.7** | **NR** | **2.2** | **2.5** |

NR: not reported

*SIR=Number of cases observed/number of cases expected

secondary to delayed screening or health care intervention for HIV-positive women and poor socioeconomic status. The overall incidence compared to the general population remains controversial with several studies suggesting a decreased overall incidence in HIV-positive populations. Lower average body weight with higher incidence of amenorrhea and decreased hormonal states may contribute to this possible decreased SIR.

### Skin Cancer

Skin cancer is one of the most frequent NADC with increased incidence of both **basal cell carcinoma** (**BCC**) and **squamous cell carcinoma** (**SCC**) variants. HIV-positive patients tend to develop skin cancers at younger ages, in non-sun-exposed areas, multiple sites at once and with increased rate of recurrence.[11] BCC are treated using a similar approach as HIV-negative patients; SCC must be approached aggressively with wide-excision margins and local or regional therapies including radiation.

## Effect of HAART on NADCs

The direct effect of HAART on NADC is controversial and may be twofold, 1) HAART can affect the overall incidence of a specific NADC, and 2) HAART can affect the prognosis of a specific NADC. The latter could be a double edged sword, since HAART can improve the immune status of HIV/AIDS patients conveying a good prognosis but sometimes can cause interactions with chemotherapy, potentially increasing the rate of adverse events or decreasing the bioavailability of the drugs.[12]

### Impact of HAART in the incidence of NADCs

In the HAART era (since 1996), the incidence of AIDS-defining cancers and other opportunistic infections have decreased dramatically; these reductions have been accompanied by a corresponding relative increase in the SIRs for NADCs. Importantly, the absolute incidence of Hodgkin lymphoma has increased significantly in the HAART era.[3] See Table 2 for the SIRs of NADC from several large-scale studies.

### Impact of HAART in the prognosis of NADCs

The impact of HAART on the prognosis of ADCs has shown an improved overall survival and decreased incidence for AIDS-defining malignancies in multiple studies. The effect of HAART on the overall prognosis for individual NADCs remains unclear. HAART may help improve local control of some malignancies and improve overall morbidity and performance status of patients potentially allowing earlier and more aggressive treatment options. These benefits of HAART appear to have limited impact on the prognosis of the majority of NADCs.

### Potential interactions between HAART and chemotherapy

HAART and chemotherapy can potentially interact due to several mechanisms, which could result in accumulation and toxicity or a decreased efficacy. However, the limited data on this topic are largely presented in case reports. Antiretroviral and chemotherapeutic agents could be substrates or inducers of the cytochrome P450 system. Several case reports have shown increased rate of toxicity with taxanes in patients receiving HAART.[13] Few cases have shown increased rate of peripheral neuropathy with *Vinca* alkaloids in patients treated for HIV-associated lymphoma.[14] Interestingly, anthracyclines do not seem to be affected by HAART.[15] These data suggest that special attention needs to be paid in HIV-positive patients undergoing chemotherapy for the arousal of unexpected and potentially dangerous adverse events.

## Conclusions

NADC are emerging malignancies that represent a new challenge for the oncologist. These patients often have aggressive disease and poor performance status, and due to their immunosuppression and ongoing antiretroviral therapy can be substrate for potential life-threatening or disabling interactions. For all these reasons, there is an increasing and unmet need for HIV oncologists familiar not only with the diagnostic but also the therapeutic aspects of the care of HIV-infected patients with malignancies. Furthermore, multi-institutional efforts, such as the NIH-sponsored AIDS Malignancies Consortium, are warranted.

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# Do Race and Ethnicity Predict Survival In Metastatic Non-Small Cell Lung Cancer?

*David Berz, MD, PhD, MPH, Katherine E. Faricy-Anderson, MD, MPH, Sherry Weitzen, PhD, Ariel Birnbaum, MD, and Gary Strauss, MD, MPH*

**Lung cancer remains the most common** cause of cancer mortality in both Rhode Island and the **United States (US).** In 2008, 880 Rhode Islanders were diagnosed with lung cancer, and 600 died from this disease.[1] Nationally, about 213,000 people were newly diagnosed and 124,000 died from lung cancer in 2007. Stage IV metastatic lung cancer is considered non-curable, and treatment with systemic chemotherapy has been shown to modestly increase quality of life and overall survival.[2,3]

A 2002 **Centers for Disease Control and Prevention (CDC)** report suggested that the overall decline in death rates of colorectal, breast, and prostate cancers was less pronounced in the African American population.[2] Another recent report suggested that African American race was a poor survival indicator in colorectal malignancies.[4] In this and other reports it was unclear if the predominant part of the survival disparities could be explained by inequalities in treatment or differences in biological disease characteristics between races.

In metastatic **non-small cell lung cancer (NSCLC),** it is not clear how race affects survival. We present an analysis of survival differences by race and ethnicity among US patients diagnosed with metastatic NSCLC.

## Methods

### Data source

The **Surveillance, Epidemiology, and End Results (SEER)** Program database from the National Cancer Institute includes approximately 26% of the United States population across several geographic regions, including all residents of CA, CT, HI, IA, KY, LA, NJ, NM, and UT, as well as the metropolitan areas of Atlanta, Detroit, and Seattle, selected rural Georgia counties and the American Indian and Alaskan Native populations in AK and AZ. SEER began collecting data on cancers diagnosed on January 1, 1973, which enables the analysis of longitudinal trends as well as current patterns of cancer. When compared with the total US population of various ethnic groups as per the 2000 US Census, SEER coverage includes 23% of all African Americans in the US, 40% of Hispanics, 42% of Native Americans and Alaska Natives, 53% of Asians, and 70% of Hawaiian/Pacific Islanders. This allows for a broad assessment of disease characteristics and health disparities across a wide spectrum of the US population. The SEER Program data are considered the international standard for cancer registry data quality. SEER data include patient demographic information as well as primary tumor site, tumor histology and differentiation and stage at diagnosis, certain details about the first course of cancer treatment, and follow up for vital status. The SEER Program obtains accurate and complete mortality data by collecting information on all deaths occurring in the US from the National Center for Health Statistics on an annual basis.

**Patients of American Indian/ Alaskan native descent had the worst lung-cancer specific survival rates.**

### Study population and outcome of interest

We included patients in the SEER registry diagnosed after 1990 with NSCLC and confirmed metastatic disease. We excluded patients with insufficient information to determine stage or histology. The outcome of interest was lung cancer-specific survival, which was determined using cause of death information provided by SEER. Survival time was expressed in months of survival after diagnosis of the malignancy. The SEER database also allows for identification of causes of death other than lung cancer. It is well known that racial disparities play a role in the mortality from certain non-malignant causes of death such as cardiovascular disease. In order to control for differences in survival introduced by racial disparities in the care for non-lung-cancer-related diseases (mainly cardiovascular disease care), patients dying from other causes were excluded from our analysis.

To evaluate for the introduction of differential attrition and selection biases, we also performed an analysis in which we removed all patients who died from causes other than NSCLC. This analysis included patients dying from causes other than NSCLC, while our final analysis excluded such patients.

### Exposure

The exposure under study was race/ethnicity, identified by SEER as non-Hispanic white; Hispanic; African American; American Indian/Alaskan Native (AI/AN); Filipino; Japanese; Chinese; Hawaiian; and "other." SEER determined race from the variable "Race1" and the **Indian Health Service (IHS)** link. When race was identified as "White" and an IHS link was identified, the person's race/ethnicity was defined as AI/AN. The NAACCR Hispanic Identification Algorithm (NHIA) was used to define Hispanic ethnicity. Persons with Hispanic ethnicity could be of any race. Persons who did not fulfill race/ethnicity criteria for non-Hispanic white, Hispanic, African American, American Indian/Alaskan Native, Filipino, Japanese, Chinese, or Hawaiian were included in the category "Other," which mainly consisted of a mix of Asian subpopulations (e.g., Korean, Vietnamese, and Thai).

### Other demographic, clinical, and pathological predictors of the outcome

Along with race/ethnicity, several other demographic, clinical, and pathological features have been described as

**Table 1. Patient Demographics and Pathologic Characteristics, N = 47,532**

| | Caucasian N=37,822 n (%) | African American N=5,430 n (%) | AI/AN N=138 n (%) | Chinese N=794 n (%) | Japanese N=598 n (%) | Filipino N=566 n (%) | Hawaiian N=353 n (%) | Hispanic N=1400 n (%) | Other N=431 n (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Period of diagnosis** | | | | | | | | | |
| 1991-1997 | 19,404 (51.3) | 2,689 (49.5) | 79 (57.3) | 374 (47.1) | 304 (50.8) | 239 (42.2) | 184 (52.1) | 673 (48.1) | 167 (38.8) |
| 1998-2003 | 18,418 (48.7) | 2,741 (50.5) | 59 (42.7) | 420 (52.9) | 294 (49.2) | 327 (57.8) | 169 (47.9) | 727 (51.9) | 264 (61.3) |
| **Gender** | | | | | | | | | |
| Male | 22,027 (58.2) | 3,537 (65.1) | 76 (55.1) | 447 (56.3) | 380 (63.6) | 384 (67.8) | 213 (60.3) | 816 (58.3) | 249 (57.8) |
| Female | 15,795 (41.8) | 1,893 (37.9) | 62 (44.9) | 347 (43.7) | 218(36.45) | 182 (32.2) | 140 (39.7) | 584 (41.7) | 182 (42.2) |
| **Marital Status** | | | | | | | | | |
| Married | 21,913 (57.9) | 2,118 (39.0) | 56 (40.6) | 562 (70.8) | 382 (63.9) | 398 (70.3) | 190 (53.8) | 791 (56.5) | 274 (63.6) |
| Divorced/Other | 15,909 (42.1) | 3,312 (61.0) | 82 (59.4) | 262 (29.2) | 216 (36.1) | 168 (29.7) | 163 (46.2) | 609 (43.5) | 157 (36.4) |
| **Age (yrs)** | | | | | | | | | |
| Median | 68 | 64 | 64 | 70 | 72 | 67 | 64 | 67 | 64 |
| Range | (21-103) | (23-101) | (36-92) | (28-98) | (30-95) | (30-96) | (29-87) | (21-99) | (26-97) |
| **Histology** | | | | | | | | | |
| Squamous | 6,659 (17.6) | 1,188 (21.9) | 32 (23.2) | 100 (12.6) | 105 (17.6) | 86 (15.2) | 76 (21.3) | 257 (18.4) | 57 (13.2) |
| Adenocarcinoma | 15,384 (40.7) | 1,981 (36.5) | 53 (30.4) | 356 (44.8) | 277 (46.3) | 271 (47.9) | 135 (38.2) | 565 (40.4) | 188 (43.6) |
| Bronchoalveolar | 549 (1.5) | 72 (1.3) | 2 (1.5) | 29 (3.7) | 12 (2.0) | 24 (4.2) | 6 (1.7) | 32 (2.3) | 14 (3.3) |
| Large Cell/Other | 15,223 (40.3) | 2,189 (40.3) | 51 (37.0) | 309 (38.9) | 204 (34.1) | 184 (32.5) | 137 (38.8) | 546 (39.0) | 172 (35.7) |
| **Differentiation** | | | | | | | | | |
| Well | 706 (1.9) | 78 (1.4) | 1 (0.7) | 20 (2.5) | 9 (1.5) | 11 (1.9) | 3 (0.9) | 33 (2.4) | 9 (2.1) |
| Moderately | 3,121 (8.3) | 429 (7.9) | 16 (11.6) | 74 (9.3) | 73 (12.2) | 52 (9.2) | 28 (7.9) | 117 (8.4) | 28 (6.5) |
| Poorly | 11,986 (31.7) | 1,689 (31.1) | 55 (39.9) | 236 (29.6) | 261 (43.7) | 214 (37.8) | 181 (51.3) | 428 (30.6) | 152 (35.3) |
| Undifferentiated | 2,306 (6.1) | 257 (4.7) | 6 (4.4) | 36 (4.5) | 29 (4.9) | 26 (4.6) | 11 (2.1) | 81 (5.8) | 20 (4.6) |
| Unusable | 19,703 (52.1) | 2,977 (54.8) | 60 (43.5) | 429 (54.0) | 226 (37.8) | 263 (46.5) | 130 (36.8) | 741 (52.9) | 222 (51.5) |

AI/AN: American Indian/Alaskan Native

prognostic markers in NSCLC. We examined gender, age, histologic subtype and marital status as other potential predictors of the outcome. During the time period of this study, the **Food and Drug Administration** (**FDA**) approved several novel chemotherapeutic agents for the treatment of metastatic NSCLC. To account for changes in available treatment regimens based on year of diagnosis, we included a variable to address the time period of diagnosis (1991-1997, 1998-2003). Although grade can be considered a relevant predictor for survival, the previous literature suggests a significant inter-rater variability when differentiation patterns are determined, i.e. tumors are graded. Hence, we excluded differentiation pattern from the analysis in our final model.

### Statistical analysis and study endpoints

We performed descriptive statistics to describe the demographic composition of the study population and the distribution of other relevant predictors of the outcome. We performed non-parametric survival analysis according to Kaplan Meier to evaluate the lung-cancer-specific survival across the different race strata and to investigate which variables were of predictive relevance. Differences along the strata of predictors of interest were evaluated using a log-rank test. If the log-rank test was statistically significant, the covariates were retained in the final model. In the final model, we performed Cox proportional hazards regression to determine hazard rate ratios. Post-estimation diagnostics were performed to analyze if the proportional hazard assumptions were violated, using graphical and computational methods. All analyses were performed using STATA 9.0 (College Station, TX).

Gender (male, female), marital status (married, not married) and time period of diagnosis (1991-1997, 1998-2003) were introduced as binary variables while age at diagnosis and histologic subtype were analyzed as continuous (age in years) and four-level variable (adenocarcinoma; bronchoalveolar carcinoma; squamous cell carcinoma; and other non-small cell histologies, which mainly consisted of large cell carcinomas), respectively.

## Results

### Baseline characteristics

Our inclusion criteria were met by 47,532 individuals diagnosed with NSCLC between 1990 and 2003. Of those, 37,822 were Caucasian, 5,430 were African American, 138 were American Indians/Alaskan natives (AI/AN), 794 were Chinese, 598 were Japanese, 566 were Filipino, 353 were Hawaiians, 1400 were Hispanics, and 431 were included in the "other" category as seen in Table 1. A higher percentage of AI/AN (57%) were diagnosed in the earlier time period of 1991-1997 as compared to Caucasians (51%), Chinese (47%), Filipinos (42%), and individuals in the "other" category (39%). In all race subgroups, we identified more men than women with NSCLC, consistent with results from previous epidemiological analyses. Overall, the majority of individuals were married. Only the African American and the AI/AN subgroups had a minority of married individuals (39% and 41%, respectively) as compared to 58% of Caucasians, 71% of Chinese and 70% of Filipinos who were married. The pathological characteristics were well-balanced, although a slightly increased incidence of favorable histologies, such as bronchoalveolar sub-types, was found in the Japanese, Chinese, and Filipinos as compared to Caucasians.

### Survival analysis

We calculated the cumulative survival for eight different racial/ethnic subgroups at one, two, and five years of follow up as well as the median overall survival in Table 2. The AI/AN population demonstrated the worst outcomes at all time points as compared with the Caucasians. The Chinese, Japanese, and Filipino subpopula-

**Table 2. One-, two- and five-year lung cancer-specific survival according to race/ethnicity**

| | 1-year OS % (95% CI) | 2-year OS % (95% CI) | 5-year OS % (95% CI) | Median OS (Months) |
|---|---|---|---|---|
| Caucasian | 14.7 (14.3-15) | 4.7 (4.1-4.6) | 0.6 (0.5-0.7) | 4 |
| African American | 14.7 (13.7-15.7) | 4.2 (3.6-4.9) | 0.3 (0.2-0.6) | 4 |
| AI/AN | 8.2 (4.2-13.9) | 2.1 (0.4-0.7) | 0 | 3 |
| Chinese | 19.1 (16.4-22) | 5.8 (4.1-8) | 1.2 (0.5-2.7) | 5 |
| Japanese | 15.3 (12.5-18.4) | 4.4 (2.8-6.7) | 0.3 (0-1.5) | 5 |
| Filipino | 18.3 (15.2-21.7) | 4.2 (2.5-6.5) | 0.7 (0.2-2.4) | 5 |
| Hawaiian | 14.5 (11-18.5) | 4.4 (2.3-7.4) | 1 (0.2-3.4) | 4 |
| Hispanic | 14.6 (12.8-16.6) | 4.5 (3.3-6) | 0.8 (0.4-1.7) | 4 |
| Other | 16.5 (13.1-20.2) | 7.9 (5.1-11.5) | 0.5 (0-2.8) | 4 |

OS: overall survival, CI: confidence interval, AI/AN: American Indian/Alaskan Native

tions demonstrated the most favorable outcomes. In univariate analyses, marital status, gender, histological subtype, age, period of diagnosis and race had a statistically significant impact on survival and were therefore retained in the final model in Table 3. The risk of lung-cancer specific death was greatest among American Indians/Alaskan Natives with a hazard ratio of 1.33 (95% CI 1.09-1.62) as compared with that for Caucasians. In contrast, the hazard ratios for the Chinese and Filipino populations were statistically significantly lower than for Caucasians, 0.84 (95% CI 0.77-0.91) and 0.80 (95% CI 0.73-0.88), respectively. African American, Hispanic, Japanese, and Hawaiian patients demonstrated similar rates of lung-cancer specific death as compared to Caucasians as shown in Table 3.

## Discussion

We present a large scale population-based analysis that demonstrates differences by race/ethnicity in disease-specific survival in US patients with metastatic NSCLC. Our study revealed several interesting findings.

First, patients of American Indian/Alaskan native descent had the worst lung-cancer specific survival rates. Previous reports have reflected an increased incidence of tobacco-related malignancies in this ethnic/racial subgroup.[5,6] These findings clearly demand further investigations of the underlying cause of this survival disparity.

Second, in this analysis, African Americans had similar rates of lung-cancer specific survival as compared with Caucasians. Previous studies have suggested that African Americans may seek medical attention at more advanced disease stages than Caucasians[7] and have been found to have a worse survival across all stages.[8] Follow up studies suggested that the racial disparities in lung-cancer specific survival were secondary to differences in performance status at presentation [7,9] and differences in surgical approaches.[10] Other studies emphasized that equal treatment resulted in equal outcomes and that being identified as African American was not an independent predictor of poor outcome in lung cancer,[11] but rather a function of differences in treatments. While this issue remains an area for further investigation, our study suggests that African American race itself does not confer a survival disadvantage.

Third, Asian subgroups had a superior survival outcome compared to all other groups. Previous reports have demonstrated that Asians with early stage lung cancer have better outcomes.[12] One prospective trial investigating combination chemotherapy of docetaxel and carboplatin identified Asian ethnicity as a positive survival indicator.[13] Recent reports have suggested that Asian subpopulations with NSCLC have a greater likelihood of responding to tyrosine kinase inhibitor therapy, including gefitinib and erlotinib, which translated into longer survival.[14] Further molecular studies have shown that certain molecular markers that predispose to a better tumor response are more common in Asians than in Caucasians.[15] However, this finding has been established specifically for newer targeted treatment strategies; our analysis predates the introduction of these therapies into the US market. Recent studies on EGFR-associated biomarkers in NSCLC specimens, however, have demonstrated that certain molecular markers also predict

**Table 3. Hazard ratio of lung-cancer specific death according to race/ethnicity**

| Racial group | Crude Hazard Ratio | [1]Adjusted Hazard Ratio |
|---|---|---|
| Caucasian | 1.0[2] | 1.0[2] |
| African American | 1.0 (95% CI 0.98-1.04) | 1.00 (95% CI 0.97-1.04) |
| AI/AN | 1.26 (95% CI 1.06-1.51) | 1.33 (95%CI 1.09-1.62) |
| Chinese | 0.88 (95% CI 0.81-0.94) | 0.84 (95%CI 0.77-0.91) |
| Japanese | 0.95 (95% CI 0.88-1.04) | 0.97 (95%CI 0.85-1.09) |
| Filipino | 0.92 (95% CI 0.84-1.0) | 0.80 (95%CI 0.73-0.88) |
| Hawaiian | 0.99 (95% CI 0.89-1.1) | 1.03 (95%CI 0.92-1.14) |
| Hispanic | 0.99 (95% CI 0.94-1.05) | 1.00 (95%CI 0.94-1.07) |
| Others | 0.93 (95% CI 0.84-1.03) | 1.01 (95% CI 0.92-1.12) |

AI/AN: American Indian/Alaskan Native

[1]Adjusted for age at diagnosis, period of diagnosis, marital status, gender, histology;

[2]Reference group

a response to "traditional" chemotherapy. The INTEREST trial[16] compared gefitinib and docetaxel in platinum-pretreated patients and demonstrated a response rate of 21% in patients with EGFR-mutant tumors, a response rate that superseded the expected rate observed in previous phase III trials.[17] Additionally, the INVITE trial, which compared single agent vinorelbine to gefitinib therapy in EGFR FISH positive pretreated patients, reported that patients in the vinorelbine arm had a superior survival.[18] This suggests that mutations and over-amplifications of EGFR, which are more common in the Asian subpopulations, may potentially improve tumor response and survival. This may explain the superior outcome of the Asian subgroups in our study.

Finally, although we detected statistically significant survival differences by racial subgroups, the median survival was dismal across all subgroups. The measurable difference between the worst performing AI/AN subgroup and the best performing Asian subgroup was only two months (3 vs. 5 months). This again emphasizes the need for more effective treatment strategies for metastatic NSCLC.

Our study has several limitations. There are inherent problems in utilizing the SEER database for analysis. First, since the information is obtained from medical documentation, the data provided by the registry is only as exact as the medical record itself. Misclassification regarding certain covariates has been reported and seems to differentially affect certain races and areas of recording. Second, the SEER database does not enable further analysis and correction for specific treatment administered. Previous studies have reported a decreased utilization of systemic chemotherapy in certain racial minorities, when compared to Caucasians. Our analysis relies on the assumption that patients are receiving comparable therapeutic regimens. Underutilization of chemotherapy might in fact have confounded our hazard ratio estimates for several racial subgroups. In addition, the SEER database does not allow adjustment for several other well-established predictors of survival in stage IV NSCLC including smoking, performance status, and newer molecular markers.

This analysis included patients diagnosed after 1990, when third-generation platinum doublet chemotherapies emerged as a standard of care for metastatic NSCLC. The currently available SEER database did not provide sufficient survival information after 2003. Therefore our analysis was not able to incorporate the potential effects on survival of more recent therapeutic developments including targeted treatments and newer chemotherapies, which may improve survival. Our analysis only included patients with stage IV NSCLC defined by metastatic disease. The revised staging system for NSCLC also classifies patients with pleural disease as stage IV.[19] We did not include this patient group in our analysis.

In conclusion, we present a large-scale study of patients with metastatic NSCLC that demonstrates significant race/ethnicity-specific differences in median survival. It must be emphasized that although we identified these statistically significant differences, median survival remains dismal across all racial/ethnic subgroups. It is imperative that we pursue further research to understand and correct the underlying disparities and work to improve survival for all of our patients with metastatic NSCLC.

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# Primary Care Concerns In Breast Cancer Patients

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**Breast cancer is the most frequent solid** tumor in women in **the United States** (**US**) and the second leading cause of cancer-related deaths. The **Surveillance, Epidemiology and End Results** (**SEER**) program of the National Cancer Institute projects 192,370 women will have been diagnosed with breast cancer in the year 2009.[1] Breast cancer incidence in the US declined by 6.7% in 2003,[2] a trend attributed to a decrease in use of **hormone replacement therapy** (**HRT**) after the Women's Health Initiative randomized controlled trial noted an excess of thromboembolic events and breast cancer secondary to HRT.[3]

Breast cancer mortality in the US has declined since 1990; this decline is thought to be due to early detection by mammography and effective adjuvant therapy.[4] Adjuvant chemotherapy reduces the annual risk of death by 38% for women younger than 50 and 20% for women age 50 to 69 years. Adjuvant endocrine therapy decreases the annual rate of mortality by 31% regardless of age for hormone receptor positive tumors.[5] Risks and benefits, patient's age and comorbid illnesses should be factored in recommendations regarding adjuvant therapy.

This review discusses prevention strategies and follow-up care of breast cancer survivors.

## Identification of patients at high risk of developing breast cancer

Breast cancer risk factors include genetic and modifiable risk factors, and 75% of patients have no risk factors. Factors that may increase the baseline risk by up to 2-4-fold are listed in Table 1. Patients noted to be at increased risk may consider the option of chemoprevention with a **selective estrogen receptor modulator** (**SERM**), such as tamoxifen.

Several tumor suppressor genes are associated with an increase in breast cancer, including *BRCA1* and *BRCA2* gene mutations. Family history may identify patients at an increased risk due to *BRCA* with the option for increased surveillance or prevention. Family history should include a careful review of paternal and maternal family history of 3-4 generations, and age of onset of malignancies in the family. Patients with family history risk factors described in Table 2, with multiple family members with breast cancer and or ovarian cancer at early age of onset should be considered for referral for genetic counseling. The increased risk of breast cancer associated with *BRCA* mutations is estimated at 57% for *BRCA1* and 49% for *BRCA2* mutation carriers and ovarian cancer risk of 40% for *BRCA1* and 18% for *BRCA2* mutation carriers.[6]

Genetic counseling includes review of family history by a certified geneticist, calculation of risk of having a gene mutation associated with an increase in cancer, and discussion of the pros, cons, cost and insurance coverage for genetic testing (approximately $3000.00). Genetic testing is not universally covered, but is usually based on a patient's risk for the gene mutatio. The genetic counselor will review with the insurer if the test will be covered. Results of testing include the presence of a deleterious mutation, absence of a mutation, or the presence of a gene mutation of unknown significance.

**Table 1. Risk Factors For Breast Cancer**

- Female gender
- Age
- Family history
- Atypia and hyperplasia
- Prior history of breast cancer
- Exogenous estrogen therapy
- Early menarche
- Late menopause
- Nulliparity

## Breast Cancer Chemoprevention

Chemoprevention trials show risk reduction benefits of 48% for invasive and/or noninvasive breast cancer with SERMs. Potential side effects associated to SERMs include an increase in thromboembolic events, cataracts and endometrial cancer. Practitioners may consider chemoprevention with a SERM such as tamoxifen for premenopausal patients and raloxifen for postmenopausal patients with a five-year projected breast cancer risk of >1.66%, (NCI breast Cancer Risk assessment tool available at http://www.cancer.gov/bcrisktool), or a history of lobular carcinoma *in situ* or atypical ductal hyperplasia. Side effects include hot flashes and increase in thromboembolic events and, for tamoxifen only, increase in endometrial cancer. The risk/benefit of chemoprevention favors

**Table 2. Consider For Genetic Counseling**

**Non-Eastern European Jewish Women**

- 3 or more first or second degree relatives at any age with breast cancer
- Breast and ovarian cancer in first and second degree relatives
- 2 first degree relatives with breast cancer, one diagnosed at or below the age of 50
- First degree relative with bilateral breast cancer
- Two or more first or second degree relatives with ovarian cancer
- History of male breast cancer
- First or second degree relative with breast and ovarian cancer

**Eastern European Jewish women**

- Any first degree relative with breast cancer or ovarian cancer
- 2 second degree relatives on the same side of the family with breast or ovarian cancer

**Table 3. Adjuvant Endocrine Therapy Side Effects**

**Tamoxifen** (pre and postmenopausal)
- Leg cramps
- Hot flashes
- Vaginal discharge
- Vaginal bleeding
- Uterine hyperplasia
- Bladder problems
- Endometrial cancer and sarcoma (rare)
- Cataracts
- Thromboembolic events

**Aromatase inhibitors** (postmenopausal)
- Hot flash
- Vaginal dryness
- Loss of bone density

women who are at low risk for thromboembolic events, women post hysterectomy and women with a higher breast cancer risk such as lobular neoplasia or atypical hyperplasia.

## Adjuvant Treatment of Invasive Breast Cancer

Breast cancer prognostic features of size, lymph node involvement, grade, hormone receptor status, patient age, and menopause status are useful to stratify the risk of systemic recurrence. Predictive factors for response to therapy include hormone receptor status, and epidermal growth factor Her-2-neu overexpression. Genetic stratification assays such as the Oncotype DX, a 21-gene recurrence score DNA array that predicts response to chemotherapy for node-negative, estrogen receptor-positive patients, have undergone prospective validation and are commercially available.[7] For Her-2-neu-positive patients, adjuvant chemotherapy and trastuzumab, a humanized monoclonal antibody directed against Her-2-neu significantly reduces the risk of systemic recurrence, with an increase in cardiac toxicity.[8]

Adjuvant therapy for estrogen receptor-positive breast cancer includes tamoxifen and, for postmenopausal women, aromatase inhibitors. Tamoxifen is associated with endometrial proliferation, hyperplasia, polyps, endometrial cancer and rare incidence of uterine sarcoma, which has a poor prognosis. The risk of endometrial cancer with tamoxifen is increased 2-3 fold. Women on tamoxifen should be monitored closely for signs and symptoms of endometrial hyperplasia or cancer, such as abnormal vaginal spotting or bleeding. The **American College of Obstetricians and Gynecologists** (**ACOG**) recommends evaluation of all potential symptoms of endometrial effects of tamoxifen in post-menopausal women.[9] Endometrial effects of tamoxifen are less likely in a pre-menopausal woman who continues to menstruate. Routine screening with transvaginal ultrasound and/or endometrial biopsy are not recommended due to the low incidence of endometrial cancer and the high rate of "false-positive" ultrasound findings of thickened endometrial stripes in the absence of significant pathology with endometrial sampling[10].

Adjuvant therapy for estrogen receptor-positive post-menopausal women includes an aromatase inhibitor for 5 years or the sequence of tamoxifen followed by an aromatase inhibitor. Common side effects of adjuvant hormonal therapy are listed in Table 3. Aromatase inhibitors prevent the conversion of androgens to estrogens by the enzyme aromatase, but do not suppress ovarian estrogen production in a premenopausal woman.

Tamoxifen is a prodrug metabolized to endoxifen by the cytochrome P450 (CYP), enzyme 2D6. Polymorphisms or drug inhibitors of CYP2D6 appear to result in low levels of endoxifen, which may impact clinical benefit from tamoxifen.[11] Assays for CYP2D6 are available, but the reliability of the commercial assays and clinical significance of patients with mutant CYP2D6 enzymes are unclear. Medications including the selective serotonin reuptake inhibitors and serotonin and norepinephrine uptake inhibitors are often prescribed to breast cancer survivors to attenuate hot flashes and depression; these drugs may also impair CYP2D6 conversion of tamoxifen to endoxifen. Patients on tamoxifen should avoid paroxetine and fluoxetine. The serotonin and norephinephrine uptake inhibitor venlafaxine is a weak inhibitor of CYP2D6 and has little effect on tamoxifen metabolism.[12]

## Primary Care follow-up after a diagnosis of Breast Cancer

There are several goals for breast cancer patient follow-up. Among them are early identification and treatment of potentially curable disease, including local breast recurrences or second primary breast cancer, adjuvant medication therapy compliance, management of treatment-related side effects, rehabilitation, and coordination of care with primary care physicians.

A routine follow-up visit by a physician trained in cancer surveillance is recommended every 3 to 4 months for the first 3 years, every 6 to 12 months for the 4th and 5th year, and then annually.[13] Additional surveillance methods can be seen in Table 4. There is no documented clinical benefit to routine CT scans, MRI, ultrasound, bone scans, positron emission tomography scanning, or blood tests other than monitoring toxicity of adjuvant therapy (common side effects of therapy are listed in Table 5) and evaluating new symptoms.

Routine patient follow-up visit includes history and review of symptoms to screen for symptoms of metastatic disease specifically presence of new or different headaches, cough, dyspnea, nausea, abdominal or bone pain, and a review of systems screening for therapy-related complications including hot flashes, vaginal discharge or dryness, dyspareunia, and depression. Mammograms should be performed 6 months after completion of radiation and then annually.

The time after a diagnosis of malignancy provides a teachable moment to address issues of overall health including

**Table 4. Follow Up of Breast Cancer Survivors**

- Evaluation by oncologist every 3-4 months for 3 years, every 6 months for years 3-5, then annually
- Breast self exam
- Mammogram
- Pelvic exam annually (tamoxifen)
- Screen for other cancers
- Bone density (aromatase inhibitors)
- Review cardiovascular risk factors

**Table 5. Complications of therapy**

**Osteoporosis**

**Risks**
- Chemotherapy
- Premature menopause
- Aromatase inhibitors

**Evaluation**
- Bone density

**Intervention**
- Exercise
- Calcium1200-1500 mg/d and vitamin D 1000 IU/d
- Bisphosphonate
- No raloxifen after diagnosis of ER positive breast cancer

**Ovarian Failure and Sexual dysfunction**

**Risks**
- Chemotherapy
- Ovarian suppression

**Symptoms**
- Hot flashes

**Intervention**
- Venlafaxine
- Gabapentin

**Symptoms**
- Vaginal dryness

**Intervention**
- Vaginal moisturizers and lubricants
- Avoid topical estrogens in patients on aromatase inhibitors

obesity, osteoporosis, second malignancies, cardiovascular disease, tobacco use, diabetes and functional decline. Oncologists and primary care physicians should encourage routine health care, cancer screening, modification in cardiovascular risk factors especially control of hypertension, smoking cessation, and glucose control. Patients should be queried annually for new family history of malignancies, specifically breast, ovarian, uterine and colon cancer, and refer to genetic counseling when appropriate (Table 2). Routine screening colonoscopies should be encouraged for women after age 50 or with a family history of colon cancer.

Cardiac disease, including **congestive heart failure** (**CHF**), is a cause of major morbidity and mortality for the older US population. Cardiac toxicity rates are higher for patients exposed to adjuvant anthracyclines chemotherapy or trastuzumab monoclonal antibody therapy for Her-2-neu gene amplification. CHF post anthracycline may be due to a "multiple hits" from chemotherapy, radiation therapy, and underlying cardiac risk factors such as hypercholesterolemia, hypertension, smoking, and diabetes. Early and aggressive treatment of hypertension with beta blockers and ACE inhibitors and other cardiac risk factors may attenuate progression to clinical CHF.

Patients prescribed adjuvant endocrine therapy have a high rate of noncompliance, including up to 50% for adjuvant tamoxifen,[14] and 25% for aromatase inhibitors.[15] The reasons can include forgetfulness, medication cost, side effects, and patient's lack of understanding of disease or benefits of therapy.[16] Practitioners are encouraged to review medication compliance, reinforce benefits of adjuvant endocrine therapy and address side effects.

A major issue for post-menopausal women on aromatase inhibitors is joint pain, which is present in up to 47% of patients[17] and is attributed to estrogen deprivation. Strategies such as switching to an alternative aromatase inhibitors and use of nonsteroidal anti-inflammatory medication may improve symptoms and compliance. The cost of oral adjuvant therapy can be addressed by the Partnership for Prescription Assistance (www.pparx.org), and other patient advocacy groups.

Sexual dysfunction and vasomotor dysfunction are common side effects of **chemotherapy-induced menopause** (**CIM**) and adjuvant endocrine therapy. These side effects include hot flashes, vaginal dryness, dyspareunia, genitourinary atrophy and decreased sexual drive. Vaginal moisturizers and lubricants can attenuate vaginal dryness and dyspareunia. Patients develop hot flashes due to CIM or adjuvant tamoxifen and aromatase inhibitors. Hot flashes may be reduced in rate and intensity with the serotonin norepinephrine uptake inhibitor antidepressant venlafaxine, the antihypertensive á-adrenergic agonist clonidine, or the anti-seizure ã-aminobutyric acid analog gabapentin.[18]

Breast cancer patients should avoid HRT and the SERM raloxifen. Adjuvant anastrozole, compared to tamoxifen results in significant loss of bone density, although patients with normal bone density prior to anastrozole did not develop osteoporosis.[19] Strategies for maintaining bone health start with a baseline bone density, adequate intake of calcium (1200mg/day) and vitamin D (800-1000 international units/day), women with low bone mineral density should have a serum 25/hydroxy vitamin D level checked and oral bisphosphonates for osteoporosis.[20] [21]

For estrogen receptor-positive patients, over half of recurrences occur after 5 years. Trials of longer duration adjuvant endocrine therapy are ongoing.


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# Why Does Rhode Island Have the Greatest Incidence of Bladder Cancer In the United States?

*Katherine E. Faricy-Anderson, MD, MPH, John P. Fulton, PhD, Anthony E. Mega, MD*

**For years, Rhode Island (RI) has had the** greatest incidence of bladder cancer in the United States for both men and women. In fact, compared with the **United States (US)** overall, all of the New England states and New Jersey have disproportionately elevated bladder cancer rates. (Figure 1) From 2002-2006, the age-adjusted incidence of bladder cancer for men was 53.1/100,000 in Rhode Island versus 37.4/100,000 in the US; for women, it was 13/100,000 versus 9.4/100,000, respectively.[1] (Table 1) In the US, urothelial (transitional cell) carcinoma accounts for about 90% of all bladder cancers. Less commonly, bladder neoplasms may be squamous cell (5%), adenocarcinoma (2%), and rarely small cell, lymphoma, or sarcoma. Because urothelial carcinoma is the predominant form of bladder cancer in the US and in RI, this review will focus on the epidemiology and risk factors of urothelial bladder carcinoma and some potential causes for the regional disparities.

## National and State Epidemiology

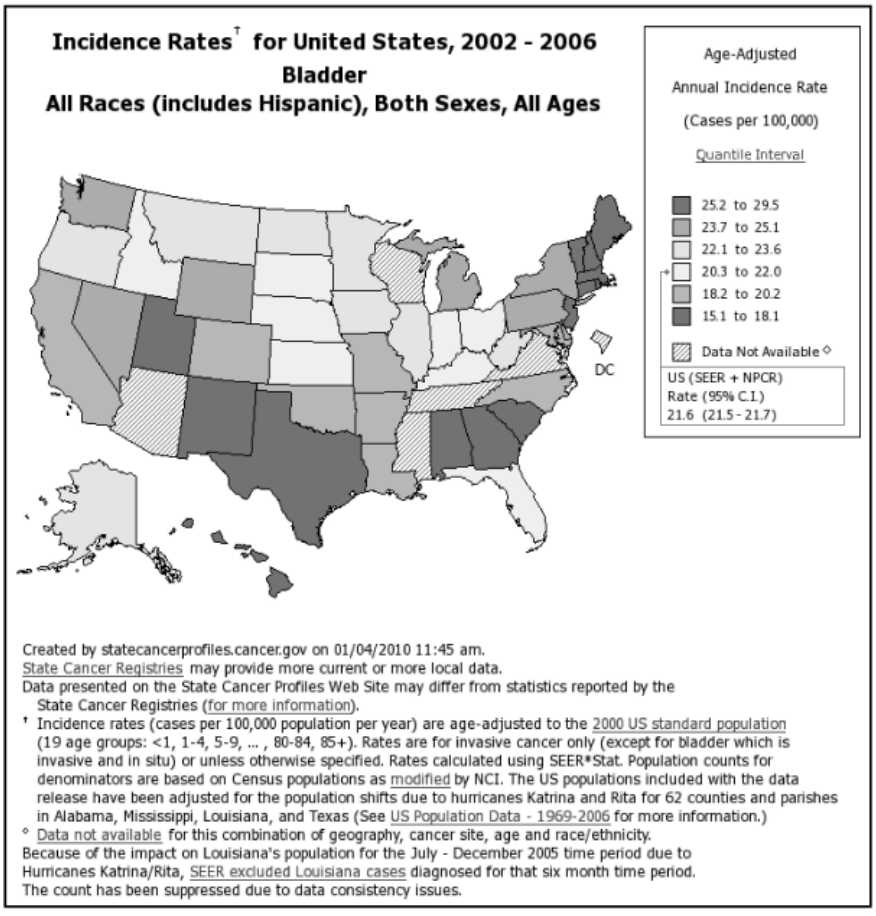
About 71,000 people (53,000 men and 18,000 women) were diagnosed with urothelial bladder cancer in the US in 2009. The median age at diagnosis was 69 years in men, 71 years in women. There were an estimated 14,000 deaths.[2] Nationally, bladder cancer is more common in men, with a 3:1 ratio of males to females. Among men, it is more common in Caucasians, with a 2:1 ratio of Caucasians to African Americans. Whether this racial disparity is due to differences in genetics, exposure patterns or other health-related behaviors remains under investigation. Although bladder cancer is more common in men and Caucasians, women and African Americans are more likely to present at later stages and have a worse prognosis.[3]

In RI, about 370 people were newly diagnosed with bladder cancer in 2008. Among Rhode Island men, bladder cancer is the fourth most common new cancer diagnosis, after prostate, lung, and colorectal cancer. Of the 6674 Rhode Islanders diagnosed with bladder cancer from 1987-2007, 73% were male and 27% female.[1] (Table 2) Most (58%) were 70 years or older, but 18% were younger than 60 years at diagnosis. The vast majority (98%) were Caucasian, which likely reflects Rhode Island's overall racial and ethnic distribution.

About 75% of urothelial cancers are diagnosed at a superficial stage and 25% are muscle invasive or metastatic at diagnosis. According to data from 2004-2007, about 77% of Rhode Island cases were diagnosed at a superficial stage, compared with 74% of US cases in that period.[1] (Table 3) This is a critical distinction because superficial cancers are generally managed with localized therapies and careful urologic surveillance. In contrast, muscle invasive or metastatic cancers may also require systemic therapy and have a worse prognosis. Unfortunately, about 80% of those with superficial disease eventually have a recurrence or progression.

Because most bladder cancers are diagnosed at an early stage, the prevalence of people living with bladder cancer is quite high. It is estimated that over 500,000 people are living with bladder cancer in the United States, with about 390,000 men and 140,000 women. In fact, among middle-aged and elderly men in the United States, bladder cancer is the 2nd most prevalent malignancy, after prostate cancer. In addition, the United

**Figure 1.**

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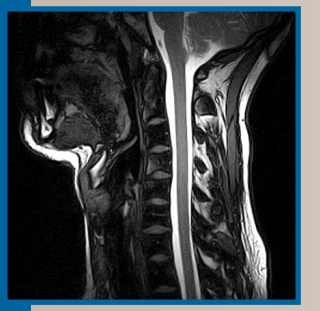

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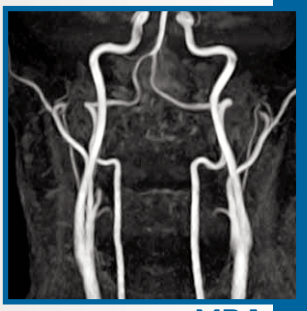

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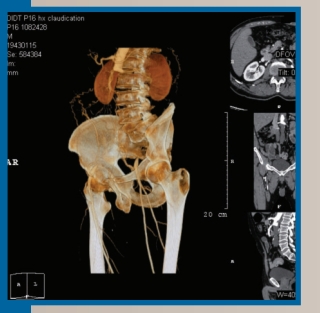

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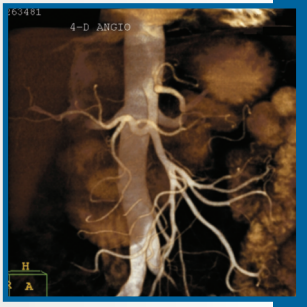


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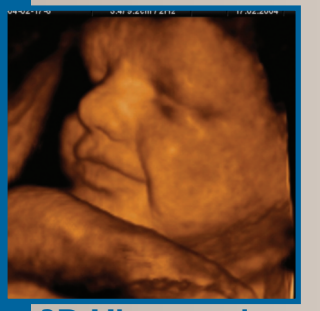

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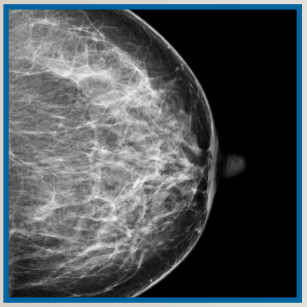

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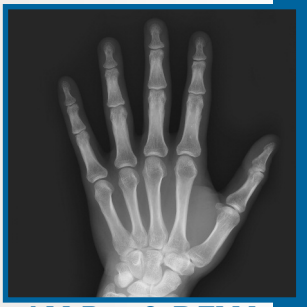

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**Table 1. Age-adjusted bladder cancer incidence rates in states with greatest incidence, 2002-2006**

| | Men | Women |
|---|---|---|
| Rhode Island | 53.1 | 13.0 |
| Maine | 49.4 | 13.4 |
| New Hampshire | 48.0 | 13.4 |
| Massachusetts | 46.7 | 12.9 |
| New Jersey | 46.2 | 12.2 |
| Connecticut | 45.4 | 12.6 |
| United States (2004) | 37.4 | 9.4 |

*Per 100,000, age-adjusted to the 2000 US standard population.

Sources: SEER (Connecticut only) and National Program of Cancer Registries

States spends about $3.7 billion per year on surveillance and treatment for patients with bladder cancer, making this one of the most expensive malignancies to monitor and treat.[4]

## Pathogenesis

As the surface epithelium lining the urinary tract mucosa, the urothelium is exposed to carcinogens excreted in the urine or activated from precursors by hydrolyzing enzymes in the urine. The latency period from carcinogen exposure to urothelial cancer development lasts from years to decades. Aberrations in either carcinogen activation or detoxification may lead to neoplastic development. Several metabolic pathways are involved in carcinogen activation, including the cytochrome P450 enzymes. Some research has shown that smokers with a genotype for extensive metabolic activation have an increased incidence of urothelial carcinoma.[5] Conversely, aberrations in carcinogen detoxification have also been implicated. For example, aromatic amines are detoxified by acetylation. "Slow" acetylators may have increased risk of cancer development, especially when faced with additional toxic exposures.[6] In addition, several oncogenes and tumor suppressor genes have been implicated in the development of urothelial carcinoma, including p53, retinoblastoma, and p16.[7]

**Table 2. Characteristics of Rhode Islanders diagnosed with bladder cancer, 1987-2007**

| Variable | Count | Percent |
|---|---|---|
| Sex | | |
| Male | 4,846 | 73 % |
| Female | 1,828 | 27 % |
| Age at Diagnosis (median) | | |
| < 50 | 478 | 6 % |
| 50-59 | 826 | 12 % |
| 60-69 | 1,585 | 24 % |
| 70-79 | 2,265 | 34 % |
| 80 + | 1,620 | 24 % |
| Unknown | 6 | 0 % |
| Race | | |
| White | 6,550 | 98 % |
| African American | 71 | 1 % |
| All Other | 53 | 1 % |

Source: Rhode Island Cancer Registry

## Risk Factors and Regional Significance

In examining the etiology of Rhode Island's persistently elevated bladder cancer incidence, it is important to consider risk factors for bladder cancer and specifically those factors that may be more prevalent in Rhode Island. Cigarette smoking and occupational exposures are the leading identified risk factors for bladder cancer in the United States and in Rhode Island. Other possible risk factors have been described (Table 4).

### Tobacco Use

The association between tobacco use and bladder cancer has been described extensively. Cigarette smoke contains numerous chemicals identified as urothelial carcinogens, including aromatic amines and polycyclic aromatic hydrocarbons. In the US, smoking is implicated in 50-60% of bladder cancer cases in men and 30% in women.[8] The rate of bladder cancer in smokers is two to three times that in nonsmokers, with long-term heavy smokers having a fivefold or more increased risk. The latency period from exposure to cancer development is thought to be 20 years or more. Smoking cessation has been found to reduce bladder cancer risk, but not to return it to baseline; a meta-analysis of eleven case-control studies found that after one to four years of smoking cessation, bladder cancer risk decreased by 35%. After 25 years, it decreased by 60%, but remained greater than that in never smokers.[8]

In 1978, the National Cancer Institute initiated the landmark **National Bladder Cancer Study (NBCS)**, the largest and most detailed bladder cancer investigation of its time. The NBCS was the

**Table 3. Stage at diagnosis by AJCC* stage groupings, Rhode Island vs. United States (SEER, 17 Registries), newly diagnosed cases of bladder cancer, 2004-2007**

| Stage at Diagnosis | Rhode Island | | United States | |
|---|---|---|---|---|
| | N | % | N | % |
| Superficial | 1,120 | 77.1 | 45,920 | 74.2 |
| Muscle Invasive | 291 | 20.0 | 13,962 | 22.6 |
| Metastatic | 42 | 2.9 | 2,009 | 3.3 |
| Total | 1,453 | 100% | 61,891 | 100% |

* American Joint Committee on Cancer

Sources: US: SEER System, via SEERStat; RI: Rhode Island Cancer Registry

first study to use data from the entire **Surveillance, Epidemiology, and End Results (SEER)** network of 10 centers, and included nearly 3000 cases diagnosed over one year and 5800 controls. Interview data examined occupational, medical, environmental, and lifestyle influences on risk. This was the first study to report excess bladder cancer risk associated not just with cigarette use but also with pipe or cigar smoking. It also found that smoking cessation was associated with a reduction in risk.[9]

According to the Centers for Disease Control and Prevention, over 50% of men and 34% of women smoked cigarettes in the US in the 1960s.[10] Although Rhode Island did not officially monitor cigarette smoking prevalence until the 1970s, local health officials have estimated that smoking rates in men in the 1950s exceeded this already high national average and remained elevated for many years. Over the last 50 years, however, Rhode Islanders have made significant progress in smoking cessation, and it is estimated that they have had below average smoking rates for several decades. Currently, Rhode Island has the 12th lowest rate of tobacco use in the country, with about 19% of men and 20% of women continuing to smoke cigarettes.[11] Given the long latency period and the persistently elevated risk of bladder cancer in former smokers, the state's historical tobacco use patterns may play a role in the elevated rates seen in more recent decades. However, this effect should attenuate with time, and it is unlikely that smoking alone is causing Rhode Island's persistently elevated bladder cancer rates.

### Occupational Exposures

Numerous studies have identified an association between certain occupational exposures and bladder cancer. Occupational exposures are thought to account for 10-20% of bladder cancers. The most compelling and consistent evidence implicates textile workers including dye users and weavers, dyestuff manufacturers, aromatic amine manufacturing workers, rubber workers, leather workers, painters, aluminum workers, and truck drivers. It is thought that occupation-related exposures to aromatic amines, including 2-naphthylamine and benzidine, are responsible for these elevated bladder cancer rates, particularly in dyestuff and rubber workers.[12] Exposure to diesel exhaust and decreased micturition have been suggested as potential risk factors in truck drivers. As with exposure to carcinogens in cigarette smoke, the latency period for these exposures is likely 20 years or more. New England has had a long history in the textile industry, and it is likely but not proven that these and other occupational exposures have contributed to our increased incidence of bladder cancer.

The **New Hampshire Bladder Cancer Study (NHBCS)** further investigated occupational and other exposure risks.[13] A population based case-control study begun in 1994 and expanded to include Maine and Vermont as the **New England Bladder Cancer Study (NEBCS)** in 2002, this study collected not just interview data but also water samples, toenail clippings, blood, and urine samples for analysis. The NHBCS confirmed the results of previous studies showing excess risk in male truck drivers, and male metal/plastics workers, after adjusting for age and smoking status. Among truck drivers, they found a positive trend of increasing risk with duration of employment. In addition, they identified excess risk in female sales clerks and female health service workers, mainly nursing aides. The etiology of these associations was unclear, but the authors postulated that decreased micturition in the former and possibly exposure to chemotherapeutic agents in the latter group could play a role. Unfortunately, this study was limited in its ability to identify workers in the specific fields of textile, rubber, leather, and aromatic amine manufacturing industries.[13]

### Water Contaminants

In addition, drinking water contaminants have been associated with bladder cancer. By-products of water chlorination, such as halogenated hydrocarbon compounds,[14] and elevated arsenic levels[15] have been associated with increased risk. A well-described bladder carcinogen, arsenic has been associated with cancers of the bladder, skin, and lung. Specifically, arsenic concentrations greater than 150 ug/L have been associated with bladder cancer, and researchers have described a dose-response relationship between arsenic levels and cancer development.[16]

Under the Safe Drinking Water Act, the US **Environmental Protection Agency (EPA)** regulates the arsenic concentration of drinking water in the United States. In response to risk assessments suggesting a link to cancers at even lower arsenic concentrations than previously thought, the EPA reduced the maximum accepted contaminant level from 50ug/L to 10ug/L.[15] While the EPA regulates arsenic concentrations in public water supplies, it has no regulatory capacity over private well use. In parts of New England, particularly New Hampshire and Maine, as many as 40% of residents use private wells. Researchers have reported elevated arsenic levels in bedrock aquifers in some regions in these states.[16] Noting these elevated arsenic levels and the fairly common use of unregulated private well water in this area, researchers hypothesized that this might be contributing to the elevated

**Table 4. Potential risk factors for bladder cancer***

| Risk Factor | Comments | Association |
|---|---|---|
| Cigarette smoking | Exposure to aromatic amines and other carcinogens (tobacco hydrocarbons, tar) | Real |
| Occupations | | |
| Aromatic amine manufacture<br>Dyestuff manufacture<br>Rubber industry<br>Painting<br>Leather industry<br>Aluminum industry<br>Truck drivers | Exposure to aromatic amines and other chemical carcinogens<br><br>Diesel exhaust or reduced bladder voiding (drivers) | Real for aromatic amine exposure, possible for others |
| Drugs | | |
| Phenacetin | | Real |
| Cyclophosphamide | | Real |
| Urinary tract infections, particularly with Schistosoma haematobium | Chronic inflammation/altered metabolism associated with squamous cell not urothelial bladder cancer | Real for *Schistosoma haematobium* |
| Carcinogens in drinking water (arsenic, chlorination by-products) | Direct carcinogenic action | Likely |
| Decreased fluid intake | Less dilution of carcinogens, decreased voiding frequency | Possible |
| Genetic polymorphisms of genes involved in aromatic amine detoxification (NAT1/NAT2, GSTM1) | Inefficient aromatic amine detoxification may lead to increased production of carcinogenic metabolites | Possible |

* Modified from **Negri E, La Vecchia C.** Epidemiology and prevention of bladder cancer. *Eur J Cancer Prevention* 2001;10:7-14.

rates of bladder cancer in New England. In fact, this was a key question posed by the NHBCS.

Unfortunately, the effects of arsenic exposure on bladder cancer risk have proven complicated to define clearly in these populations. In analyses completed to date, the NHBCS has found no association between arsenic exposure and bladder cancer risk among never smokers. However, among smokers, those smokers in the uppermost arsenic exposure category did demonstrate a non-statistically significant excess risk (OR 2.17, 95% CI 0.92 – 5.11).[17] Research is ongoing to better define this potential interaction. Other researchers have also suggested that tobacco use may enhance the carcinogenic effect of arsenic exposure. In addition, researchers are investigating the potential role of DNA methylation and other epigenetic events which may be associated with increased bladder cancer risk.

While arsenic from well water remains a possible contributor to elevated bladder cancer rates in Rhode Island, it seems unlikely that it contributes significantly if at all. While 30-40% of New Hampshire residents rely on private well water, only about 10% of Rhode Islanders do. In addition, Rhode Island does not appear to have the elevated levels of arsenic in bedrock aquifers found in parts of northern New England. Other potential sources of arsenic exposure include soil contamination and pressure-treated lumber. In most areas with elevated arsenic levels, this has been associated with prior land use, including arsenic-containing pesticides at former orchard sites. Currently, the public water sources are in compliance with the state's regulations on safe arsenic levels, and there is no evidence to suggest that the 10% of residents who obtain water from private wells have elevated arsenic levels in their water, although this data is not currently monitored.

### Iatrogenic Factors

Cyclophosphamide, a chemotherapeutic agent often used to treat non-Hodgkin's lymphoma, is an established bladder carcinogen with a dose-dependent relationship. One case-control study reported a four-fold increased risk of bladder cancer and an absolute risk of between three and seven excess cancers, depending on cumulative doses, per 100 non-Hodgkin's lymphoma patients after fifteen years of follow up.[18] Pelvic irradiation for prostate, ovarian, and cervical cancer has been associated with a 1.5 to four times increased risk of bladder cancer and a latency period of only five to ten years.[19] Historically, heavy use of phenacetin-containing analgesics has been associated with increased risk of cancer of the bladder, renal pelvis, and ureter, prompting its classification as a carcinogen in 1987 and its removal from most of the European countries and the United States.

## Additional Factors

Decreased fluid intake has been associated with increased bladder cancer incidence. In the Health Professionals Follow Up study with 48,000 participants, those who drank <1.3 liters of fluid daily had twice the risk of bladder cancer as those who drank over 2.5 liters daily.[20] Chronic bladder irritation has been implicated in the development of squamous cell bladder cancer, rather than urothelial carcinoma. Classically, infection with *Schistosoma haematobium* has been associated with squamous cell bladder cancer, likely due to chronic bladder inflammation. In regions with endemic schistosomiasis, such as the Middle East, Asia, and Africa, most bladder cancers are squamous cell carcinomas, rather than urothelial carcinomas. Similarly, some data have shown that spinal cord injury patients with neurogenic bladder may be at increased risk of squamous cell bladder cancers.[21]

In that Rhode Island welcomes many new residents each year, it is important to consider not only local factors but also exposures in recent immigrant populations. Currently two of the largest immigrant populations are Hispanics and Africans.[1] New residents may bring both old and new exposures with them, and environmental factors elsewhere may affect cancer incidence in our state. On the basis of current immigration patterns, there is no reason to expect a great impact on our current trends in bladder cancer incidence, but this remains another factor to monitor.

## Conclusions

In summary, Rhode Island has the greatest incidence of bladder cancer in the nation. The cause of this disparity remains unproven, although compelling explanations have emerged. The two historical exposures that appear to have had the greatest impact are high rates of tobacco use and specific occupational exposures. Given the very long latency period of bladder cancer development, it is likely that we are continuing to see the delayed effects of these exposures. The impact of arsenic and other water contaminants on our state's bladder cancer incidence appears to be small, if any, and any effects they may have are likely to be constant over time. Research is ongoing in this area.

As Rhode Island's rates of tobacco use and specific occupational exposures have significantly declined in the last several decades, the magnitude of their combined effects should attenuate with time. If these truly are the main factors influencing our currently elevated bladder cancer incidence rates, then we predict that these rates will level off and start to decline over the next several years to decades. We will continue to monitor these trends vigilantly. Realizing that a heightened awareness of bladder cancer risk could translate into increased surveillance and increased detection of superficial cancers, we will also continue to monitor trends in the stage at which these cancers are diagnosed. Bladder cancer continues to have a significant impact on the health of Rhode Islanders, and we will continue to investigate ways to better understand and reduce this burden for our residents.

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# The Evolving Role of Histology In the Treatment of Non-Small Cell Lung Cancer

*Naveed Rana, MD, and Humera Khurshid, MD*

**Lung cancer is the second most common** type of cancer (after prostate in men and breast in women) and a major cause of cancer-related mortality.[1,2] An estimated 222,520 new cases of lung cancer are expected in 2010, accounting for about 15% of cancer diagnoses. The incidence rate is declining significantly in men, from 102.1 cases in 1984 to 71.3 cases per 100,000 in 2006. In women, the rate is approaching a plateau after a long period of increase.[2] Lung cancer accounts for more deaths than any other cancer in both men and women. An estimated 157,300 deaths, accounting for about 28% of all cancer deaths, are expected to occur in 2010.[2]

## Histology

**Non-small cell lung cancer** (**NSCLC**) accounts for approximately 85% of all lung cancers. These are subcategorized as adenocarcinoma (44%), squamous cell carcinoma (23%), large cell (4%), and not otherwise specified (28%).[3] Adenocarcinomas mostly involve peripheral airways and are the most common subtype in never-smokers. They metastasize frequently, and are associated with mutations in the K-RAS gene and the **endothelial growth factor receptor** (**EGFR**). Squamous cell carcinomas typically arise in more central airways, have stronger association with tobacco smoking and have high levels of **thymidylate synthetase** (**TS**) and increased expression of ERCC1.

For decades the differentiation of lung cancers for the purpose of treatment was made on the basis of NSCLC versus **small cell lung cancers** (**SCLC**). The standard of care for unresectable, locally advanced and metastatic NSCLC is platinum-based duplet therapy combined with newer third-generation agents the standard of care. This was supported by multiple trials done during the 1980s and early 2000s. One such trial compared four platinum-based doublet regimens in 1100 patients;[4] a modest overall survival benefit of approximately 8 months was seen among all groups. An older phase III study did not show a difference in survival comparing four different chemotherapeutic regimens.[5] Another trial by Scagliotti et al[6] compared **gemcitabine and cisplatin** (**GC**), **carboplatin and paclitaxel** (**PCb**) with **vinorelbine and cisplatin** (**VC**) in locally advanced or recurrent/metastatic NSCLC and showed no significant differences in response rate or overall survival with either of the combinations. A retrospective subgroup analysis of this study failed to show that histology was predictive of outcomes in either of the PCb, GC or VC arms.[7]

This approach is starting to shift. Recently, histology is being used to guide therapy. Some chemotherapy drugs have shown to be more effective while others are associated with increased rates of adverse events in certain histological subgroups of NSCLC. For example, pemetrexed, an antifolate cytotoxic drug, is more effective in the non-squamous cell group both in chemo-naive patients as well as second line and maintenance settings; and the newer anti-VEGF inhibitors (bevacizumab) and **epidermal group factor receptor** (**EGFR**) **tyrosine kinase inhibitors** (**TKIs**) are associated with increased toxicity in patients with squamous cell histology.

## NSCLC Histology and Efficacy (Table 1)

Scagliotti et al[8] conducted the largest phase III randomized non-inferiority study comparing GC versus **cisplatin plus pemetrexed** (**CP**) in 1725 patients with untreated advanced NSCLC. Non-inferiority was documented because the median survival time was an identical 10.3 months in each arm. Progression-free survival and objective response rates were also comparable. Interestingly, for the first time histology demonstrated a role in predicting response to a cytotoxic chemotherapy combination as among the 847 patients with adenocarcinoma, CP had median overall survival of 12.6 compared to 10.9 months in the CP arm (p=0.03). In contrast, the opposite was seen for the 473 patients with squamous cell carcinoma, with survival favoring the CG arm compared with the CP arm (p>0.05). There was statistically significantly more grade 3 to 4 granulocytopenia, thrombocytopenia, and anemia and increased febrile neutropenia associated in the gemcitabine-containing arm.

Similar results were seen when single-agent pemetrexed was compared with docetaxel in a randomized phase III trial for second line treatment of advanced NSCLC. This non-inferiority trial established the role of pemetrexed in the second line setting. Overall response rates of 9.1% vs. 8.8% and median survival of 8.3 versus 7.9 months were seen with pemetrexed and docetaxel, respectively.[9] A retrospective analysis using subset histology data showed better survival with pemetrexed for non-squamous group comparing with docetaxel, and once again the reverse was true for squamous cell histology.[10]

**Table 1. Selected studies on the role of NSLC histology of chemotherapy efficacy**

| Study | Design | Regimen | Overall Survival (months) | |
|---|---|---|---|---|
| | | | Non-Squamous | Squamous |
| Scagliotti [8] | Phase III | Cisplatin/pemetrexed | 11.8 | 9.4 |
| | First line | Cisplatin/gemcitabine | 10.4 | 10.8 |
| Peterson [10] | Retrospective | Pemetrexed | 9.3 | 6.2 |
| | Second line | Docetaxel | 8.0 | 7.4 |
| Ciuleanu [11] | Phase III | Pemetrexed | 15.5 | 9.9 |
| | Maintenance | Best supportive care | 10.3 | 10.8 |

RR: response rate, PFS: progression free survival OS: overall survival

Maintenance therapy with pemetrexed has also shown improved progression-free survival versus placebo for advanced lung cancer of non-squamous NSCLC patients that did not progress after 4 cycles of platinum-based duplet chemotherapy. In a phase III double blind study, 663 patients were randomly assigned to receive pemetrexed plus best supportive care versus placebo and best supportive care every 21 days until disease progression. Pemetrexed significantly improved PFS 4.3 versus 2.6 months ($p<0.0001$) and overall survival 13.4 months versus 10.6 months ($p=0.12$). Subgroup analysis again showed that when comparing with placebo, progression free survival (PFS) was superior in the non-squamous group (4.5 vs. 2.6 months, $p=<0.00001$) than squamous cell (2.8 vs. 2.6 months, $p=0.039$) and objective response rate was also better for non-squamous than the squamous cell group.[11]

The significant treatment-by-histology interaction indicates that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others in the trials. One hypothesis is the higher expression of TS in squamous cell carcinomas compared to non-squamous histology. TS is one of the main target enzymes of pemetrexed and its higher expression in squamous cell cancers possibly makes them resistant to pemetrexed therapy which in turns leads to decreased efficacy as compared to non-squamous non-small cell histology. This hypothesis is based on *in vitro* studies showing over expression of TS correlates with reduced sensitivity to pemetrexed.

## NSCLC Histology and Safety (Table 2)

Bevacizumab is a humanized **anti-vascular endothelial growth factor (VEGF)** antibody, which exert a direct antiangiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional antitumor activity may be obtained via the effects of bevacizumab on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells. Bevacizumab has been studied in phase II and III trials in combination with standard platinum-based duplet therapy, and it has been approved by FDA as a first line agent for non-squamous NSCLC.

This approval is based on the higher incidence of pulmonary hemorrhages in patient with squamous NSCLC. In a phase II trial,[12] chemo-naive patients with stage IIIB or IV NSCLC were treated with PCb versus PCb and bevacizumab. Six patients (9%) in the bevacizumab groups had pulmonary hemorrhage and four of them were fatal. Subset analysis showed that 31% of these episodes occurred in squamous cell group whereas only 4% occurred in non-squamous group. In a randomized phase III study (ECOG 4599),[13] platinum-based duplet therapy with or without bevacizumab was evaluated; 878 patients with recurrent or advanced non-squamous NSCLC (stage IIIB or IV) were assigned to chemotherapy with PCb alone or PCb plus bevacizumab. Chemotherapy was administered every 3 weeks for six cycles, and bevacizumab was administered every 3 weeks until disease progression was evident or toxic effects were intolerable. Median OS was significantly improved (12.3 vs. 10.3 months, respectively) with significant improvement in response rates (35% vs. 15%) and PFS (6.2 vs. 4.5 months). Clinically significant bleeding was about 4.4% in bevacizumab group compared with 0.7% in controls. Another study (AVAiL)[14] evaluated the combination of CG and bevacizumab versus CG and placebo as first line agent for advanced non-squamous NSCLC. Response rate and median PFS were better in the bevacizumab-containing group; however, the incidence of fatal pulmonary hemorrhage was approximately 1%.

**Table 2. Selected studies on the incidence of bleeding complications with bevacizumab**

| Study | Regimens | Hemoptysis | Life-threatening pulmonary hemorrhage |
|---|---|---|---|
| Sandler [13] | Carboplatin/pemetrexed | 0.5% | 0.2% |
| | Carboplatin/pemetrexed + Bevacizumab 7.5 mg/kg | 2.1% | 1.6% |
| Manegold [14] | Cisplatin/gemcitabine | 4.9% | 0.3% |
| | Cisplatin/gemcitabine + bevacizumab 7.5 mg/kg | 7% | 1.2% |
| | Cisplatin/gemcitabine + bevacizumab 15 mg/kg | 9.7% | 0.9% |

## Emergence of Tyrosine Kinase Inhibitors and Their Relation To Histology

The EGFR family is part of a complex signal transduction network that is central to several critical cellular processes. About 10% of NSCLC respond to EGFR-targeted TKIs. More than 75% of "responders" have activating mutations in EGFR and EGFR sequence analysis is a useful method for predicting response and PFS following TKI therapy in NSCLC.[15] The **Food and Drug Administration (FDA)** has approved the EGFR TKIs gefitinib and erlotinib for the treatment of advanced NSCLC.

A phase III open-label study (IPASS) randomly assigned previously untreated patients from East Asia with advanced NSCLC to receive gefitinib or PCb; 1217 patients with stage IIIB/IV lung cancer of adenocarcinoma etiology, non-smokers of former light smokers were included in the study. The primary end point was PFS. EGFR mutation data for 437 patients (36%) could be evaluated, 261 (60%) were positive for a mutation. The median PFS was 5.7 months in the gefitinib group and 5.8 months in the PCb group and 12-month PFS were 24.9% and 6.7%, respectively. In the EGFR mutation-positive subgroup, PFS was significantly longer among patients receiving gefitinib than among those receiving PCb ($p<0.001$).[16]

Erlotonib has also been evaluated in the second and third line settings and lead to its inclusion as therapeutic armamentarium against NSCLC. Over 700 patients received erlotinib or placebo in a randomized trial and showed a response rate of 8.9% with a 2-month improved

overall survival as compared to placebo. Bronchioalveolar carcinoma had the best response rate of 25% and, interestingly, severity of skin rash, a common side effect of EGFR TKIs, was strongly associated with higher survival rates.[17]

Sunitinib is a tyrosine kinase inhibitor and has shown some activity in a phase II trial of previously treated stage IIIB/IV NSCLC patients; ORR was 11% with overall survival of 23 weeks. Toxicities included life-threatening hemorrhage in 3 patients (2/23 squamous and 1/40 adenocarcinoma).[18]

## Conclusion

The term NSCLC is no longer sufficient with regard to treatment selection, and according to the data abovementioned, we have few perspectives. First, we believe that for non-squamous NSCLC, the combination of cisplatin and pemetrexed with or without bevacizumab is emerging as a preferable chemotherapeutic regimen. However, this combination has not been investigated formally against many of the most commonly used combinations. Second, in a much selected group of patients with EGFR mutation-positive adenocarcinomas, gefitinib or erlotinib can be considered as a first line agent. Data show that it is inappropriate and potentially harmful to give TKI to a patient whose EGFR mutation status is unknown.[19] Patients receiving erlotinib upfront who are EGFR mutation-negative have worse survival and cannot be rescued with chemotherapy. Third, patients with squamous cell lung cancers are not suitable for treatment with cisplatin and pemetrexed due to lower efficacy or for treatment with bevacizumab-containing regimens due to safety issues. Finally, many other molecular targets (HER-2, EML4-ALK) are being evaluated for targeted therapy, which have shown some promise in phase II trials. The treatment of advanced metastatic NSCLC is evolving, and researchers are testing different, novel drugs and personalizing chemotherapeutic combinations.

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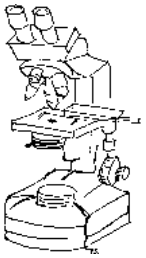

# The Creative Clinican

## A New Low for an Old High: Neutropenia Induced by Levamisole-Adulterated Cocaine

*Andrew Van Wieren, Mahim Kapoor, MD, Pooja Rao, MD, and Rebekah Gardner, MD*

**Recently, both the media and medical literature have directed** attention towards neutropenia associated with levamisole-adulterated cocaine. Levamisole, available in South America as an anti-helminthic veterinary agent, was previously used in the **United States (US)** for treatment of colon cancer and rheumatoid arthritis. Due to its well-established adverse effect of reversible neutropenia in approximately 20% of patients exposed,[1] levamisole was voluntarily removed from the US market in 2000.[2] Despite this known complication, levamisole has been isolated in up to 70% of cocaine seized by the **Drug Enforcement Administration (DEA)** in recent years.[3] Evidence suggests traffickers in supply countries adulterate cocaine with levamisole, likely due to a known stimulatory synergism between the two drugs.[2,4]

Since 2009, nearly 100 cases of neutropenia associated with levamisole-adulterated cocaine have been reported in medical literature in North America and Europe. These patients, variably testing positive for cocaine and/or levamisole, have presented with symptoms including fever, generalized lymphadenopathy, oral ulcers, opportunistic infections, retiform purpura and, in at least one case, death.[1-3,5-8] Exposure to levamisole can be tested by urinary gas chromatography, but this assay is not widely available and is of limited utility given the short urinary half-life of levamisole (5-6 hours).[1-2] While the exact mechanism of levamisole-induced neutropenia remains unknown, reports of HLA-B27, lupus anticoagulant and **anti-neutrophil cytoplasmic antibody (ANCA)** positivity among neutropenic patients exposed to levamisole suggest a potential autoimmune pathophysiology.[1,8,9] G-CSF has been proposed as a treatment to shorten the duration of levamisole-induced neutropenia and minimize associated complications, but its relative efficacy for this purpose has not been firmly established.[1]

### Case

A 64-year old man with a history of alcohol and cocaine abuse presented with three days of cervical lymphadenopathy, painful oral ulcers, sore throat and anorexia. He reported nasal and oral use of approximately 5g of cocaine in the previous month, but denied any other constitutional symptoms, exposures, past medical history, or medications.

Vital signs were within normal limits. Pertinent physical exam findings included oral candidiasis, tender nasopharyngeal ulcerations, submandibular and anterior cervical lymphadenopathy, normal cardiopulmonary exam, absence of hepatosplenomegaly or rash, and normal neurologic exam. Laboratory findings showed severe neutropenia (ANC 200), but normal hemoglobin, platelets, serum chemistries, LFTs, urinalysis and CXR. Urine toxicology was positive for cocaine.

The patient was admitted for workup of his neutropenia and lymphadenopathy, and management of the nasopharyngeal lesions and candidiasis. He was treated with fluconazole and empiric broad-spectrum antibiotics and given supportive care. Infectious workup was negative for Gonorrhea and Chlamydia, HIV, HCV, CMV, VZV and B19 Parvovirus, but revealed equivocal EBV and HBV titers (negative on follow-up). Chest and abdominal CT scans were negative for malignancy. Rheumatologic workup demonstrated positive c-ANCA, proteinase-3 and lupus anticoagulant antibody, but negative p-ANCA, ANA and RF. The patient exhibited neither signs nor symptoms of Wegener's granulomatosis and denied history of thrombosis. His positive c-ANCA and proteinase-3 serologies were attributed to cocaine-induced midline nasal disease, and the positive lupus anticoagulant antibody was ascribed to levamisole exposure—associations reported previously in the literature.[1,10] Given his history and otherwise negative workup, it was concluded that, despite negative urinary levamisole gas chromatography, his isolated severe neutropenia was likely due to use of levamisole-adulterated cocaine. Over his two-week hospital course, his ANC slowly resolved to 1800 on discharge without G-CSF treatment, with improvement of the candidiasis and lymphadenopathy.

### Discussion

Approximately 2.39% and 4.11% of the US and RI adult populations, respectively, reported cocaine use within the past year in 2006 and 2007. RI ranks second only to the District of Columbia.[11] Given the high rate of cocaine use within RI and pervasive contamination of the cocaine supply with levamisole,

| Results of urinary toxicology tests | Cocaine positive (half-life = 3-4 days) | Cocaine negative |
|---|---|---|
| Levamisole positive (half-life = 5-6 hours) | -Almost certain | -Possible, but confusing |
| Levamisole negative | -Probable (this case)<br>-Lupus anticoagulant Ab? | -Possible (with history), but less likely |

**Table 1:** Is this *otherwise unexplained* neutropenia due to levamisole-adulterated cocaine? Results from urinary toxicology tests for cocaine and levamisole can aid clinicians in diagnosing neutropenia induced by levamisole-adulterated cocaine (based on WHO-UMC system for standardized case causality assessment) [12]

health care workers in RI should maintain a high index of suspicion for levamisole exposure among patients.

This case of probable levamisole-induced neutropenia illustrates several important considerations. When encountering patients with neutropenia of unknown etiology and/or a history of cocaine use, clincians should take a thorough history. That history should include questions about recent cocaine or crack use. If a patient's history or physical exam suggests cocaine exposure, a urinary toxicology screen and levamsole gas chromatography should be ordered quickly, given the short half-lives of both cocaine and levamisole (3-4 days and 5-6 hours, respectively).[2] This case corroborates prior evidence that lupus anticoagulant antibody can play a role in confirming levamisole exposure in urinary levamisole-negative patients,[1] but further studies are needed to establish the positive predictive value, specificity, and clinical implications of the antibody in this clinical context.

Notably, a positive history of cocaine use does not definitively indicate levamisole ingestion because not all cocaine is contaminated, and there appears to be regional variation in the prevalence of levamisole-tainted cocaine.[3] Similarly, confirmed ingestion of levamisole does not exclude the presence of other more common causes of neutropenia. As evidenced by this case, given the short urinary half-lives of cocaine and levamisole, patients with negative urinary levamisole and/or cocaine levels could conceivably have levamisole-associated neutropenia if the exposure were outside of the urine toxicology screen window. Levamisole-induced neutropenia should remain a diagnosis of exclusion, reserved for cases in which other causes of neutropenia have been ruled out and clinical suspicion, in conjunction with laboratory data, is particularly suggestive. Table 1 depicts how cocaine, levamisole and lupus anticoagulant antibody test results can inform clinical suspicion of levamisole-associated neutropenia.

G-CSF has been identified as a potential treatment for levamisole-induced neutropenia, but is generally not begun until other causes of neutropenia have been excluded.[1] This case underscores the clinical challenge in making this diagnosis, and subsequently, the decision to initiate treatment. Waiting for laboratory results to return can delay treatment, leading to lower neutrophil counts, longer hospital stays, additional morbidity and mortality, and ultimately higher health care costs. In patients presenting with neutropenia of unknown etiology, more widespread and timely screening for cocaine, levamisole and lupus anticoagulant antibody could expedite treatment with G-CSF, if appropriate.

Further studies are needed to identify: 1) the prevalence of levamisole in the cocaine supply; 2) the incidence of levamisole-induced neutropenia from cocaine use; 3) the sensitivity and specificity of urinary levamisole and lupus anticoagulant antibody as diagnostic tests; 4) the therapeutic efficacy of G-CSF in treating patients with neutropenia in the setting of cocaine use, after other common etiologies are excluded; and 5) the natural history and associated morbidity and mortality of confirmed levamisole-associated neutropenia.

The US Government's **Substance Abuse and Mental Health Services Administration** (**SAMHSA**) has issued a nationwide public health alert regarding levamisole-adulterated cocaine, and encourages clinicians to report suspected and confirmed cases to state health departments or local Poison Control Centers.[3] We encourage hospitals and health centers to educate physicians and staff, who should in turn inform at-risk patients, their communities, and the popular media regarding yet another dangerous complication of cocaine use.


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# Nutrition Recommendations for the Independent-Living Older Person

*Brenna Brucker, Lynn McNicoll, MD, Renee Shield, PhD*

**Up until her 83rd birthday, Mrs. had steadfastly refused to** comply with dietary recommendations for her diabetes. She continued to boil her oatmeal in sugar-water and meet her friends daily at a local bakery for pie.

However, after a bout with a urinary tract infection exacerbated by uncontrolled blood sugar, Mrs. W agreed to see the nutritionist. She wanted to continue living independently and explained that she had been resistant because she did not want to drastically change her lifestyle. Now, on her 83rd birthday, she was ready to listen.

## Nutrition and Health

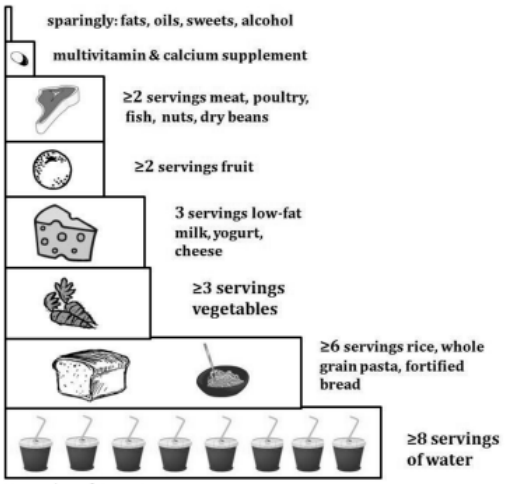
Independence is based on mobility and cognitive function; the ability to go where you want, remember what you want to do when you get there, and carry out your intended activities. High function in old age is achieved by maintaining a healthy weight, observing proper nutrition, and maintaining or even improving muscle strength. Gentle changes to lifestyle, such as taking a multivitamin, taking short walks, or joining a water aerobics class, can have a substantial impact on preserving independence. Often, independently living older persons do not have calorie malnutrition but do have macronutrient and micronutrient deficiencies. Overall health, especially mobility, is dependent on maintaining a healthy weight.

Older persons typically experience weight gain because they are less active and have less metabolic need, yet consume the same caloric amount as when they were more active. This weight gain can lead to less mobility and premature mortality. High protein foods, such as low-fat dairy and meat products, are linked to fewer regained pounds post weight-loss. In an ongoing large randomized controlled study at eight different European centers, preliminary data showed that higher protein content enhanced weight loss and prevented regaining the lost weight.[1] Dietary calcium decreases fat absorption, and a sufficient intake may also prevent excessive hunger during weight loss diets.

However, older persons sometimes experience unintentional weight loss. Physicians should monitor the elderly patient for a weight loss of more than ten pounds or 10% of body weight in six months. If this loss was unintentional, it may be due to several conditions; e.g., depression, hyperthyroidism, ill-fitting dentures, undiagnosed cancer, and occult infection. Weight loss from increasing exercise can be healthy because muscle is built as fat is lost. However, weight loss from anorexia and immobility can lead to loss of muscle and the risk of falls.

Sometimes it is difficult to choose foods that are high in nutrients, low in calories, and inexpensive. Meals on Wheels is a national organization that uses local volunteers to deliver hot meals to many independent older persons; (Sidebar: RI Nutrition Resources) however, not all meals meet individual taste preferences. This is true for other community nutrition pro-

**Figure: Nutrition recommendations for older persons over 70[4]**




Examples of 1 serving:
Water: 1 cup. Carbohydrate: 1/2 cup of cooked cereal, rice, or pasta, 1 slice of bread, 1 ounce of ready-to-eat cereal. A normal dinner-sized portion of spaghetti would count as 2-3 servings. Vegetable: 1 cup of raw leafy vegetables, 1/2 cup of non-leafy vegetables (cooked or chopped raw), 3/4 cup of vegetable juice. Dairy: 1 cup of milk or yogurt, 2 ounces of processed cheese. Fruit: 1 medium apple, banana, orange, 1/2 cup of chopped, cooked, or canned fruit, 3/4 cup of fruit juice. Meat and nuts: 2-3 ounces of cooked lean meat, poultry, or fish, 1/2 cup of cooked dry beans, 1 egg, 1/3 cup nuts. Fats, oils, sweets, alcohol: No serving sizes because these items should be consumed in very small quantities. The number of servings one should consume is based on how many calories the individual needs; the lowest number of servings in each category is based on a 2,000 calorie/day diet.

[4] Russell RM, Rasmussen H, et al. Modified Food Guide Pyramid for People over Seventy Years of Age. *J. Nutr* 1999;129(1):751-3.

Table: Key Points in the treatment of nutritional issues for Independent-Living Older Person

| | Lab Test | Recommendation to Patient |
|---|---|---|
| Nutrition | Albumin, prealbumin | (Figure: Nutrition recommendations) |
| Vitamins | Blood test for vitamins D, B12, methylmalonic acid, homocysteine levels, and folate | Take a multivitamin plus an additional calcium supplement daily (goal: 1500 mg calcium/day with 800 IU vitamin D) |
| Hydration | Blood urea nitrogen and creatinine | Drink 8 glasses of water per day, even if not thirsty unless contraindicated |
| Exercise | Creatinine Phosphate, Kinase | Resistance training for 15 minutes every day, focusing on quadriceps and triceps<br>Walk, swim, or water aerobics for 30 minutes every day |

grams. This can lead to older persons either not eating enough to receive sufficient nutrients or choosing primarily low-cost, low-nutrient, convenient snack foods, in order to feel full. Furthermore, lifelong eating habits can be difficult to change. Several sets of guidelines recommend a balanced diet such as the food pyramid (Figure: Nutrition recommendations).

## Vitamin Supplements

Most geriatricians believe that multivitamins are important, cost very little, and carry little if no risk. These geriatricians believe that multivitamins are justified in all elderly populations (not just those losing weight or with absorption problems) because it is extremely difficult to ensure that each meal contains essential nutrients while fighting the constraints of budget, availability, time, taste preference, and caloric balance (not exceeding the recommended calories for the day). Multivitamins contain the recommended daily allowance of most of the major vitamins, including vitamins D, B6, and B12 (to guarantee macronutrient and micronutrient sufficiency) at $15 - $35 per year if taken once daily.

Some multivitamins may contain several times the recommended daily allowance of vitamin B12, which is harmless even

## RI NUTRITION RESOURCES

**Delivered Meals and Sit-down Meal Sites:**

**RI Meals On Wheels** www.rimeals.org (401) 351-6700
- Daily deliveries to over 2,000 homes; waiting lists vary
- For those unable to cook, living alone, 60 years old or older, and homebound
- Suggested donation of $15.00 per week
- Example main entrée: potatoes, rice or pasta, a vegetable, milk or juice, bread, dessert and occasional salad.
- "Diabetic," finely chopped and kosher meals also available

**The Ocean State Senior Dining Program** www.dea.ri.gov/programs/food_assistance.php (401) 847-7821
- Hot nutritious lunches M-F for older or disabled individuals at 75+ meal sites
- Small donation encouraged
- Transportation available with 24 hours notice

**Senior Centers** www.providenceri.com/senior/centers.php
- Majority of Senior Centers provide hot lunches, outreach, transportation and health services
- Website with calendar of events for most RI senior centers: www.seniordigestnews.com/Calendar/tabid/1528/Default.aspx

**Food Delivery Services and Nutrition Access:**

**RI's extensive network of online grocery ordering and delivery:** www.online-grocery-shopping.net

**Ask Rhody** www.askrhody.org
- Rhode Island's social service website, which provides information on all services for seniors in RI

**Eldercare Locator** www.eldercare.gov 1-800-677-1116
- Free national service that will connect seniors with people who will set up home-delivered meals, transportation, legal advice, adult day care, home health services and housing options

**Senior Nutrition Awareness Project (SNAP)** http://www.rimeals.org/special-programs/snap
- Free nutrition hotline (1-800-595-0929) for seniors with questions about food or nutrition; registered dietitians provide information by phone and mail
- Offers free nutrition newsletters, recipes, educational videos and fact sheets
- Provides free nutrition workshops in senior centers and offers educational material to borrow

**AARP** http://www.aarp.org (401) 248-2671
- Produces booklets and tapes and a monthly magazine with nutrition, drug and health information

**Senior Companion Program** (401) 462-0569
- Volunteers assist frail, isolated older adults in their homes, adult day centers and community sites
- Offer pleasant company for dining, socializing or help in receiving food delivery

at much higher doses. B12 deficiency can lead to dementia; in the US, more than 15% of people over sixty years old have a B12 deficiency.[2] In some, this deficiency is due to age-related gastric atrophy and hypochlorhydria or use of a proton-pump inhibitor, resulting in reduced gastric acid and less efficient absorption of vitamin B12 from foods. Nonetheless, crystalline vitamin B12 found in supplements can be absorbed even if there is a malabsorption syndrome; therefore, oral supplementation is usually sufficient. Clinicians should also consider monitoring methylmalonic acid and homocysteine.

In multivitamins, the dose of vitamin E is well below the levels reported to cause an increase in overall mortality, the dose of vitamin A is too small to increase risk for fractures and osteopenia, and the dose of beta-carotene (usually a part of the total vitamin A activity) is well below levels associated with lung cancer.

Multivitamins typically contain less than half the recommended levels of calcium and vitamin D. The recommended dose in older persons is 1500 mg calcium accompanied by 800 IU vitamin D. In summary, older persons should take a multivitamin plus an additional calcium supplement daily, to ensure adequate calcium and vitamin D (Table: Key Points).

## Hydration

To maintain weight and observe proper nutrition, it is as vital to stay hydrated and follow a high fiber diet as it is to take supplements. Kidney function declines with age, as does the ability to detect thirst. For healthy older adults without contraindications, it is recommended that they should drink eight or more glasses of water or juice every day to reduce stress on the kidneys, prevent delirium, and help maintain normal bowel function. However, older people often restrict their hydration to limit trips to the bathroom, minimize incontinence accidents, and reduce the risk of falls on the way to a bathroom.

## Exercise

Sarcopenia (Greek, *sarx* -flesh, *penia*- loss) is an age-related progressive loss of muscle mass. It is associated with decreased mobility and increased falls, fractures, and nursing home admissions. Sarcopenia is easy to diagnose in underweight older persons but is often overlooked in older persons with high body mass indexes. Overweight older persons can have legs that look strong, yet are only adipose tissue and bone, with such significant sarcopenia that a fall is imminent. Sarcopenia is associated with the loss of type II fibers.[3] However, with age, type I fibers hypertrophy. To maximize muscle, older persons should exercise every day, consume more than two servings of protein per day, and minimize periods of bed rest.

To preserve muscle, the recommendation is to promote resistance training for fifteen minutes each day, optimally every day of the week, concentrating predominately on quadriceps extension, but also on triceps extension (maintaining "get up and go"). Low impact exercise for thirty minutes per day is optimal to protect cardiovascular health, enhance mood, maintain bone density, improve balance and gait, as well as counteract the age-related increase in fat and decrease in skeletal muscle. Even minimal exercise (such as, walking, Wii, exercise bike, gardening) can be beneficial, as well as improve mood and outlook.

## Back to Mrs. W

A month after her visit to the nutritionist, Mrs. W began to check her blood sugar and watch her diet. Most important, Mrs. W convinced her friends to join her three times a week for a water aerobics class (instead of pie); this activity increased her motivation as well as maintained her social network. The extent of social relationships is a powerful predictor of functional status and mortality. Preserving mobility and cognition by maintaining a healthy weight, observing appropriate nutrition, and exercising are cornerstones to healthy aging, almost as important as having somewhere to go and a purpose for going there.

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# Prepregnancy Obesity and Birth Defects In Rhode Island

*William Arias, MPH, and Samara Viner-Brown, MS*

**Obesity is a chronic condition linked with diabetes, stroke,** coronary artery disease, and hypertension. [1] The estimated prevalence of obesity in the United States (26.7%) and Rhode Island (24.9%) has increased over the past decades.[2,3] Obese women are at increased risk for pregnancy complications and poor birth outcomes. Specifically, prepregnancy obesity has been associated with birth defects, especially neural tube defects and congenital heart defects. [4] However, less is known about the relationship of obesity with birth defects in Rhode Island.

## Methods

A case-control study was conducted among Rhode Island births during 2007-2009. Cases were defined as newborns born during 2007-2009 at Women & Infants Hospital (Providence, RI) and Kent Hospital (Warwick, RI) with at least one diagnosed birth defect. A birth defects case was identified using ICD-9 (International Statistical Classification of Diseases, 9th Edition) codes 740-759, and 760.71. Controls were defined as Rhode Island resident births born in 2007-2008 with no diagnosed birth defect. Controls were taken from the Rhode Island **Pregnancy Risk Assessment Monitoring System (PRAMS),** a survey that asks new mothers about behaviors and experiences before, during and after pregnancy.

Prepregnancy obesity was based on height (cm) and prepregnancy weight (kg) of the mother to calculate a body mass index (kg/cm$^2$). Obesity is defined as having a **body mass index (BMI)** >30. Height and pre-pregnant weight data for cases were collected through prenatal care documents via medical chart review. Height and prepregnant weights for controls were collected from PRAMS survey responses (self-reported data). Cases and controls that did not have both maternal height and/or prepregnant weight data were excluded. Demographics for cases and controls were examined and significant differences were identified for analytical adjustment. To compare population characteristics between study cases and controls, weighted PRAMS percentages were calculated to reflect Rhode Island population distribution.

Data were analyzed by birth defects body systems (cardiovascular, musculoskeletal, etc.). The cardiovascular birth defects body system was further classified into structural groups of congenital heart defects (conotruncal, septal, and obstruction). Logistic regression was used to analyze the relationship between prepregnancy obesity and birth defects outcomes, controlling for diabetes mellitus and low birth weight to produce an adjusted **odds ratio estimate (aOR).** Pre-gestational diabetes was collected through medical chart review for the cases and collected through PRAMS responses for the controls. Gestational diabetes was not included in this analysis since it develops during pregnancy. Low birth weight is defined as less than 2,500 grams (~5.5 lbs). Statistical analysis was performed using SAS software.

## Results

Of the 1,317 potential birth defects study cases for 2007-2009, 995 (76%) had maternal heights and prepregnancy weights for BMI calculation, and were included in the study. Among 2,668 PRAMS respondents from 2007-2008, 2,521 (95%) had maternal heights and weights for BMI calculation. Among this group, 2,344 (93%) did not have a birth defect, and were included in the study.

Table 1 Demographic Characteristics of Study Cases and Controls

| Variable | Cases (n=995) n (%) | Controls (n=2344) n* (%**) |
|---|---|---|
| Obese (BMI ≥ 30) | | |
| *Yes* | 233 (23.4) | 503 (17.1) |
| *No* | 762 (76.6) | 1841 (82.1) |
| Diabetes | | |
| *Yes* | 31 (3.1) | 102 (1.7) |
| *No* | 963 (96.9) | 2242 (96.3) |
| Birth Weight | | |
| *Low BW* | 162 (16.3) | 928 (7.2) |
| *Normal BW* | 833 (83.7) | 1416 (92.8) |
| Gestational Age | | |
| *Preterm* | 192 (19.3) | 714 (8.4) |
| *Term* | 799 (80.3) | 1621 (91.4) |
| Sex | | |
| *Male* | 599 (60.2) | 1145 (51.4) |
| *Female* | 394 (39.6) | 1193 (48.6) |
| Maternal Age | | |
| *< 20* | 115 (11.6) | 227 (10.5) |
| *20 - 34* | 680 (68.3) | 1690 (72.9) |
| *> 34* | 200 (20.1) | 419 16.6) |
| City/Town | | |
| *Core**** | 493 (49.5) | 1219 (47.9) |
| *Non-Core* | 502 (50.5) | 1009 (52.1) |
| Race/Ethnicity | | |
| *White* | 578 (58.1) | 1427 (57.0) |
| *Black* | 134 (13.5) | 225 (9.4) |
| *Hispanic* | 233 (23.4) | 454 (20.3) |
| *Native* | 5 (0.5) | 29 (1.4) |
| *Asian* | 33 (3.3) | 103 (2.8) |
| *Other* | 12 (1.2) | 37 (1.7) |
| Insurance | | |
| *Public* | 509 (51.2) | 1102 (47.1) |
| *None* | 15 (1.5) | 18 (0.4) |
| *Private* | 470 (47.2) | 1210 (47.7) |
| Education | | |
| *< 12th* | 194 (19.5) | 376 (16.3) |
| *12th* | 271 (27.2) | 671 (29.6) |
| *> 12th* | 461 (46.3) | 1167 (49.1) |
| *Unknown* | 69 (6.9) | 130 (5.0) |

**Unweighted PRAMS numbers*
***Weighted PRAMS percentages*
****Towns with more than 15% of children live in poverty*

Table 2 Association between prepregnancy obesity and birth defects in Rhode Island, 2007-2009

| | Cases (n) | Unadjusted | Adjusted* | p-value |
|---|---|---|---|---|
| Overall birth defects | 995 | 1.12 (0.94 - 1.34) | 1.18 (0.98 - 1.42) | .07 |
| NBDPN 45 anomalies** | 473 | 1.30 (1.04 - 1.63) | 1.38 (1.09 - 1.74) | **.008** |
| Cardiovascular defects | 235 | 1.37 (1.01 - 1.86) | 1.43 (1.05 - 1.95) | **.02** |
| septal heart defects | 157 | 1.34 (0.93 - 1.93) | 1.38 (0.95 - 2.00) | .09 |
| conotruncal heart defects | 62 | 1.88 (1.10 - 3.20) | 1.88 (1.09 - 3.24) | **.02** |
| obstruction heart defects | 21 | 1.83 (0.75 - 4.56) | 2.07 (0.83 - 5.16) | .11 |
| Orofacial defects | 28 | 1.73 (0.78 - 3.86) | 1.96 (0.88 - 4.36) | .10 |
| Genitourinary defects | 145 | 1.00 (0.66 - 1.50) | 1.03 (0.67 - 1.57) | .90 |

* Pre-gestational diabetes and low birth weight (≤ 2500 g)

** 45 congenital anomalies selected by the National Birth Defects Prevention Network

Table 1 shows the population characteristics of study cases and controls by selected demographics. Among 995 birth defects cases, 233 (23.4%) were obese prior to becoming pregnant. This is higher than the controls, where 17.1% were obese prior to their pregnancy. Low birth weight and preterm delivery rates among the cases (16.3% and 19.3%, respectively) were more than twice the rates of the control group (7.2% and 8.4%, respectively). There were a higher proportion of males among the case group (60.2%) compared to the controls (51.4%). Other demographic variables such as maternal age, core city status, and maternal education show a fairly similar population distribution across specific subpopulations among cases and controls.

Table 2 shows the measures of association between pre-pregnancy obesity and selected birth defects groups adjusted for diabetes and low birth weight. A subset of 45 birth defects categorized as severe and important by the **National Birth Defects Prevention Network** (www.nbdpn.org) shows an aOR of 1.38 (1.09 – 1.74). Cardiovascular defects also show a relationship with prepregnancy obesity with an aOR of 1.43 (1.05 – 1.95). After classifying these cardiovascular defects into three congenital heart defects groups (septal, conotruncal, and obstruction), conotruncal heart defects showed a higher degree of association with prepregnancy obesity (aOR = 1.88, CI 1.09 – 3.24) than the other heart defects groups. There were no significant findings among other body system groups such as orofacial and genitourinary defects.

## Discussion

Conotruncal defects are a group of congenital heart defects that show the strongest association with pre-pregnancy obesity in this study. During the 4th week of gestation, a fetal structure called the conotruncus is formed. This structure is the basis for the development of main vessels connecting to the heart, which can lead to their subsequent birth defects outcomes such as transposition of great vessels and truncus arteriosus. The close temporal proximity of the conotruncus to prepregnancy obesity exposure provides a stronger link than with birth defects that arise from other fetal structures occurring later in fetal development. Another study has also shown a link between severe obesity and conotruncal heart defects.[5]

Research has shown that diabetes is strongly associated with birth defects.[6] Although adjusting for diabetes is necessary to find an association with pre-pregnancy obesity and birth defects, it was used with caution for this analysis since there was a small sample of diabetics among cases. Diabetes was also slightly higher among the controls than cases, presenting a problem for this study to control for diabetes.

Although there was enough power to conduct this study with all birth defects, the sample size was insufficient to analyze small groups of birth defects (e.g., obstruction heart defects and neural tube defects). Also, different data collection methods were used for cases (nurse reporting via medical charts) versus controls (self-reported questionnaire). There was also variation in the percentage of subject exclusion due to missing heights and pre-pregnancy weights and therefore, insufficient BMI information, among cases (25%) and controls (5%). Lack of recording heights and prepregnancy weights in prenatal care documents may be due to varying prenatal care practices.

This study and other research show that women who are obese prior to their pregnancy are at greater risk for having a baby with a birth defect. It is therefore important for women to be educated prenatally about the risks of pre-pregnancy obesity on birth outcomes.

In addition to concerns about obesity and its impact on maternal and child health, there are also medical costs related to maternal obesity and birth defects. Obese pregnant women have more prenatal fetal tests, ultrasound examinations, and prenatal visits than pregnant women of normal weight.[7] Hospitalization costs incurred among women who give birth to children with birth defects are seven times higher than women who give birth to children with no birth defects.[8]

Primary care providers, obstetricians and gynecologists, and other health care providers can play a critical role in educating women of reproductive age about the importance of achieving a healthy weight prior to becoming pregnant.

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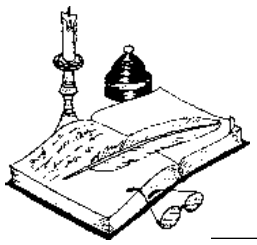

# Physician's Lexicon

## From Catheters to Cathedrals

**The catheter is a hollow surgical tube** employed to drain fluids—typically urine—from an interior cavity of the body. The word is derived from a Greek root, *cata/catha-*, translated as "something let down" and is cognate with the Latin, *jacere*, meaning to throw, to spurt forth, as in the English, ejaculation.

The cathode, the negative pole of a battery, uses the Greek prefix, *cata-*, meaning downward, and appears in related words such as catabolism, cataclysm, catacomb (underground cemetery), catalepsy, catalogue (to count the words down), catalyst (able to go down, to dissolve), cataract (a falling of the water; and used to describe ocular opacities because they sometimes emerge as an obscuring shade resembling a waterfall).

The *cata-* root has also come to signify downwardness, as in cleaning or purifying or "getting down to fundamentals." A catharsis, accordingly, is defined as a purging, paradoxically a liberation of the emotions, and pharmacologically as an intestinal purgation or cleansing. Catatonia, describes a severe form of schizophrenic dementia and is often highlighted by episodes of stupor and muscular rigidity. The *–tonia* root is also from a Greek word meaning to stretch or produce tension. The derivative Latin, *tendere*, also means to stretch.

A catastrophe is defined as a disastrous happening, a terrible mishap, a downfall. It also uses the prefix, *cata-*, signifying the sense of going down and the Greek root, *strophe*, meaning a twisting or turning as in English words such as apostrophe and strophanthin.

The adjective, catholic, is a fusion of the Greek *catha-* , and *holos* (meaning entire or total, as in words such as holograph), thus offering the meaning of universal.

The word cathedral is a shortening of the phrase, *ecclesia cathedralis,* meaning the seat of a bishop. A *cathedra*, in Greek, indicates a contrivance to sit down, a chair. And the phrase, *ex cathedra*, means from the chair, and, by further inference, from the chair of someone, such as a bishop, a person in authority. The phrase, *ex cathedra*, has come to indicate any authority, secular or ecclesiastic.

A scattering of additional nouns use the *catha/cata-* prefix. The Catharists—meaning those who are spiritually cleansed—were a medieval sect of Christians centered in southern France. The feminine name Catherine signifies one who is cleansed, pure. But Cathay, a poetic name for China, is derived from a Tartar word possibly meaning kingdom.

– Stanley M. Aronson, MD

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# Vital Statistics

Edited by Colleen Fontana, State Registrar

## Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

| Underlying Cause of Death | Reporting Period | | | |
|---|---|---|---|---|
| | October 2009 | 12 Months Ending with October 2009 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 192 | 2,337 | 222.4 | 3,147.5 |
| Malignant Neoplasms | 204 | 2,259 | 215.0 | 6,317.5 |
| Cerebrovascular Diseases | 46 | 420 | 40.0 | 787.0 |
| Injuries (Accidents/Suicide/Homicde) | 47 | 574 | 54.6 | 9,548.5 |
| COPD | 37 | 521 | 49.6 | 292.5 |

| Vital Events | Reporting Period | | |
|---|---|---|---|
| | April 2010 | 12 Months Ending with April 2010 | |
| | Number | Number | Rates |
| Live Births | 1,005 | 12,183 | 11.4* |
| Deaths | 799 | 9,098 | 8.5* |
| *Infant Deaths* | (5) | (78) | 6.4# |
| *Neonatal Deaths* | (4) | (65) | 5.3# |
| Marriages | 313 | 6,118 | 5.7* |
| Divorces | 291 | 3,235 | 3.0* |
| Induced Terminations | 396 | 4,231 | 347.3# |
| Spontaneous Fetal Deaths | 91 | 720 | 59.1# |
| *Under 20 weeks gestation* | (84) | (644) | 52.9# |
| *20+ weeks gestation* | (7) | (76) | 6.2# |

(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 1,050,788

(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, October 1920

In "Encephalitis Lethargica," Charles A. McDonald, MD, reported on the cases that he had examined. In spite of much research, "it is fair to say the cause has yet not been discovered." Although encephalitis lethargica and poliomyelitis are similar ("It may be that one is an attenuated form of the other") the "weight of evidence is that these diseases are not identical." Dr. McDonald described a woman who had been asleep for five days. Eventually she died without waking. Dr. McDonald estimated the mortality rate at 7 to 10%.

An Editorial, "Narcotics Clinics," noted the end of the "clinics for narcotic habitués, which have been in operating…since the passage of the Harrison Anti-Narcotic Act." The editor judged the clinics to have been the "dispenser of drugs, rather than a means of cure of the habitué." The editor judged outpatient treatment ineffective. The new solution for drug addiction was to be the State Hospital at Howard.

A second editorial, "A New Specialty," described the emergence of "industrial surgery," tied to large industrial organizations.

## Fifty Years Ago, October 1960

Americo A. Savastano, MD, contributed "Low Back Pain from the Orthopedic Standpoint." He cited the principal points to consider in a diagnosis: pain, tenderness, muscle spasm, limitation of motion, posture, tests of passive mobility, x-ray and laboratory tests.

Henry C. McDuff, Jr, MD, contributed "Gynecological Causes of Backache.

Ernest K. Landsteiner, MD, contributed "Urological Causes of Back Pain."

In "Western Equine Encephalomylelitis in Rhode Island," Alton M. Paull, MD, and Raymond Young, PhD, described the incidence in animals, then concluded with a report of a patient "thought to represent the first case of western equine encephalitis diagnosed in this state and probably in New England."

Mieczyslaw Garber, MD, reported on "The Use of an Aldosterone Antagonist in Patients with Resistant Edema." He discussed two patients.

## Twenty-Five Years Ago, October 1985

In "Competency Peer Review," Herbert Rakatansky, MD, explained the Medical Society's Peer Review Competency Committee and the Impaired Physicians Committee disciplinary board.

Mark J. Fagan, MD, and Tom J. Wachtel, MD, in "Serum Iron Studies Compared to Bone Marrow Iron in Patients with Pernicious Anemia," explained: "Unless transferrin is less than 25%, bone marrow biopsy is essential to exclude iron deficiency."

Rosalind Ekman Ladd, PhD, and Edwin N. Forman, MD, in "Pediatric Ethic Rounds: An Evaluation," noted: "The impact of ethics rounds on clinical decision-making is worthy of further exploration."

In "Controversies in the Treatment of Parkinson's Disease, Joseph Friedman, MD, noted: Carbidopa-levodopa combination is effective, but not without problems and complications."

H. Denman Scott, MD, and John T. Tierney contributed "Home Care in a Hectic Envrionment."





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