Cancer Surveillance Research

Cancer Epidemiology, Biomarkers & Prevention

International Trends in Liver Cancer Incidence Rates

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Abstract

Background: Several previous studies have documented region or country-specific liver cancer incidence trends around the world. However, no study has systematically examined the international pattern using the most recently updated incidence data from the International Agency for Research on Cancer.

Methods: We examined recent trends in liver cancer incidence rates from 1993 to 2002 by joinpoint analysis for 32 cancer registries worldwide, using Cancer Incidence in Five Continents. We also examined the male to female rate ratios for these and four additional registries, based on the 1998–2002 incidence data.

Results: Liver cancer incidence rates for both men and women statistically significantly increased from 1993 to 2002 for 8 of 32 cancer registries considered in the analysis. Increases were largely confined to economically developed countries of Western Europe, North America, and Oceania. In contrast, rates decreased in both men and women in 5 registries including 3 in Asia. Despite this, the incidence rates in Asian countries are twice as high as those in Africa and more than four times as high as rates in North America. Male to female rate ratios varied from 0.9 in sub-Saharan African and South American registries to 5.0 in France and Egypt.

Conclusions: Liver cancer incidence rates continue to increase in some low-risk parts of the world whereas they are decreasing in some of the highest risk countries in Asia. Etiologic studies are required to further elucidate factors contributing to the divergent liver cancer incidence trends worldwide.

Impact: Our description of international liver cancer incidence trends may stimulate further etiologic studies. *Cancer Epidemiol Biomarkers Prev; 20(11); 2362–8. ©2011 AACR.*

Introduction

Liver cancer is the sixth most commonly diagnosed cancer worldwide with an estimated 749,700 new cases in 2008 (1). The vast majority of primary liver cancers, 75% to 90%, are hepatocellular carcinomas (HCC), which are malignant tumors of liver parenchymal cells. The other primary liver cancer is intrahepatic cholangiocarcinoma (ICC), a tumor of cells lining bile ducts (2). There is wide variation in international liver cancer incidence rates mainly due to the geographic variation in HCC, which is primarily associated with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, but is also linked to other risk factors such as dietary aflatoxin exposure, alcohol-related cirrhosis, fatty liver disease, obesity, smoking, diabetes, and iron overload (3–5). Although ICC only represents 10% to 25% of primary liver cancers in most parts of the world, it is the most frequent subtype of liver cancer diagnosed in Thailand due to the extremely high prevalence of chronic liver fluke infestation, the major risk factor for ICC (2). Cirrhosis is also an important risk factor for ICC (6).

Previous studies from a variety of international sources have reported trends in liver cancer incidence rates, including increasing trends in developed countries with historically low liver cancer incidence rates and decreasing trends in areas with the highest observed liver cancer incidence in the world (7–11). However, these studies were limited because they were country- or region-specific (8–11) or because they were based on old data sets (7). In this article, we present the contemporary variation in liver cancer incidence patterns across 5 continents by examining incidence rates provided by the International Agency for Research on Cancer (IARC) for 32 select cancer registries around the globe over a 10-year time period (1993–2002). We also present the difference in liver cancer incidence rates between men and women for the 32 registries and 4 additional registries as well as age-specific rates for select registries, based on the 1998–2002 incidence data.

Methods

Liver cancer incidence rates by year for select cancer registries worldwide were obtained from IARC's

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org).

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doi: 10.1158/1055-9965.EPI-11-0643

Cancer Incidence in Five Continents (CI5) databases (12). The CI5 series aims to provide data on cancer incidence from populations all over the world for which high-quality data are available; therefore, data sources vary and include national registries (e.g., Czech Republic, New Zealand), local registries [e.g., Murcia (Spain), Miyagi (Japan)], or combinations of local registries (e.g., 9 SEER registries which we used to represent the United States; ref. 13). Two CI5 databases are available: CI5 I–IX which contains aggregated data over 5 years as they appeared in the 9 volumes of CI5, and CI5*plus* which contains annual long-term incidence data for a single registry or group of registries in a country (13). We restricted our trend analysis to 32 cancer registries or combined registries included in CI5*plus* that have incidence data beginning in 1988 and did not have a zero case value for any given year; however, for rate ratio comparisons between the sexes we also used data from 4 additional African and Asian registries available in CI5 I–IX for broader geographic representation.

We examined trends in liver cancer incidence rates from 1993 through 2002, using joinpoint regression analysis, which involves fitting a series of joined straight lines on a logarithmic scale to the trends in the annual rates. The resulting trends of varying time periods are described by annual percent change (APC), that is, the slope of the line segment (14). The method is described in detail elsewhere (14). To facilitate comparison across countries and between men and women, a summary measure, the average APC (AAPC), was calculated and the resulting trends from this analysis are discussed throughout this article. The AAPC is estimated as a geometric weighted average of the joinpoint APC trend analysis, with the weights equal to the lengths of each segment during the specified time interval (15). In describing the change, the terms "increase" or "decrease" were used when the AAPC was statistically significant, otherwise the term "stable" was used. We also examined longer term trends (1988–2002) using joinpoint analysis, allowing a maximum of 2 joinpoints and the results of this analysis are presented in Supplementary Table S1. In addition to describing the incidence trend, we examined the difference in liver cancer incidence rates between men and women in the most recent time period (1998–2002) by calculating the ratio of incidence rates in women to that in men and providing 95% confidence intervals (95% CI) around the resulting rate ratios. We also examined age-specific incidence rates for select cancer registries during the time period 1998–2002 to assess differences in the liver cancer burden by age in different populations.

All rates were age-standardized to the 1960 world standard population to compare data across countries and over time with different age compositions. Liver cancer incidence data in the CI5*plus* database are categorized according to International Classification of Diseases (ICD)-10 codes (C22) as are data used from the most recent volume (IX) of CI5 I–IX (12).

Results

Overall incidence rate trends

Liver cancer incidence rates statistically significantly decreased for both men and women from 1993 through 2002 for 5 of 32 cancer registries considered in the analysis and increased for 8 of the 32 cancer registries (Fig. 1). The decreases occurred primarily in Asia whereas the increases occurred primarily in Western Europe, North America, and Oceania.

The largest increases in liver cancer incidence from 1993 to 2002 occurred in the United Kingdom where rates increased 6.2% and 6.9% per year among men and women, respectively (Fig. 1). Other Western European registries with increasing liver cancer incidence among men and women included Saarland (Germany) and France (8 registries). In Northern and Eastern Europe liver cancer incidence generally remained stable or slightly increased. Two notable exceptions are Sweden and Poland (2 registries) where decreasing rates were observed. Liver cancer incidence rates among men and women decreased 1.6% and 2.3%, respectively, per year in Sweden and 4.5% and 5.7%, respectively, per year in Poland (2 registries) from 1993 through 2002.

In North America and Oceania, liver cancer incidence rates increased in all registries examined, including the United States (SEER 9), Canada, Australia, and New Zealand, with the highest increases in Australia where rates rose 4.3% per year in men and 6.3% per year in women from 1993 through 2002 (Fig. 1). However, liver cancer incidence trends were more varied in South America. Incidence rates remained stable in both men and women in Columbia (Cali) and Ecuador (Quito), whereas in Brazil (Goiania) rates remained stable among men but decreased 7.1% per year among women from 1993 through 2002. In contrast, liver cancer incidence rates in Costa Rica increased 5.0% and 6.0% per year among men and women, respectively, during the same time period.

In Asia, where liver cancer incidence rates are among the highest worldwide (Table 1), decreasing rates for both men and women were observed for 3 of the 7 registries or group of registries examined including China, the Philippines, and Japan (Fig. 1). Incidence rates remained stable among both men and women in Israel (Jews), Chiang Mai, Thailand, and Singapore (Chinese). In India, liver cancer incidence remained stable among men but increased among women from 1993 through 2002 (Fig. 1). The trends based on 15 years of data (1988–2002) are generally similar to the trends based on 10 years of data (Supplementary Table S1).

Incidence rates by age

Liver cancer incidence rates increased with advanced age in all 5 registries examined [China (Qidong County), Zimbabwe (Harare), Costa Rica, the United States (SEER 9), and Sweden]. However, rates for Qidong County, China were extremely high and far exceeded the observed age-specific rates in the other 4 registries at every age

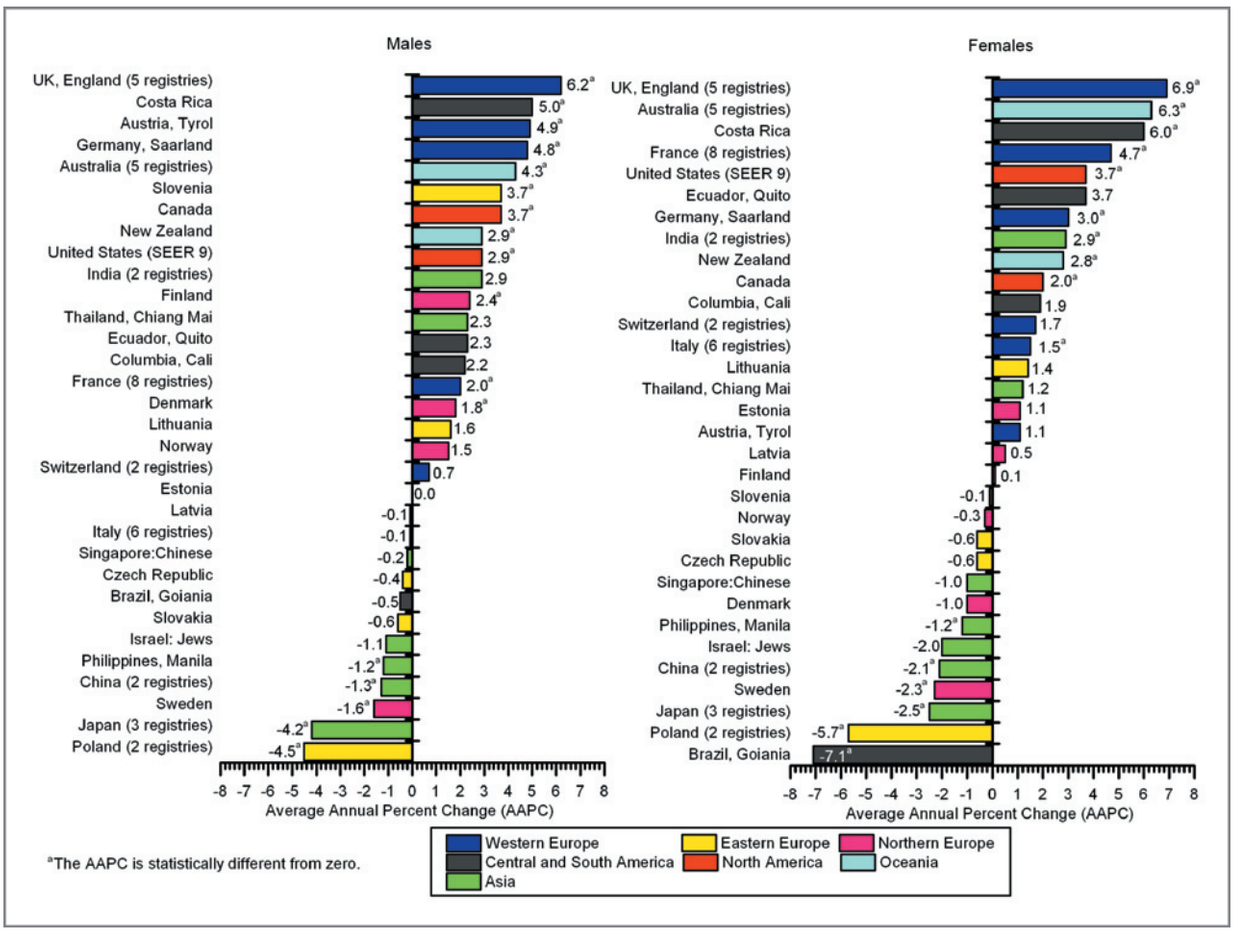

Figure 1. Liver cancer incidence trends among males and females in select registries, 1993–2002, CI5.

category beyond age 29. In Qidong County, China, the male liver cancer incidence rate (per 100,000) for the 45- to 49-year age group in 1993–1997, the most recent years for which data are available, was nearly 30 times as high as the rates for the corresponding age and sex in the United States, Costa Rica, Sweden, and Harare (Zimbabwe) in 1998–2002 (Fig. 2).

Incidence rates by gender

By sex, liver cancer incidence rates were generally higher during 1998–2002 among men than in women. Male to female rate ratios remarkably varied across regions worldwide from 0.9 to 5.0 (Table 1). The highest rate ratios occurred in some high-risk/high-rate areas such as Egypt, Singapore, Korea, and China and in low-risk/lower-rate areas of Europe such as France, Switzerland, and Slovenia. The lowest male to female rate ratios were observed in registries of South America [Costa Rica and Columbia (Cali)] and Africa [Uganda (Kampala) and Zimbabwe (Harare)]. Quito, Ecuador was the only registry for which liver cancer incidence rates were higher, albeit nonsignificantly, for women than for men (Table 1).

Discussion

Liver cancer incidence rates increased from 1993 through 2002 for both men and women in 8 of the 32 cancer registries included in this analysis. The increases were generally observed in developed countries, particularly those in North America, Western Europe, and Oceania, that reported among the lowest liver cancer rates worldwide. In contrast, decreasing liver cancer incidence rates were observed in 5 of the 32 cancer registries, largely confined to registries in Europe and Asia with 3 of the registries (China, the Philippines, and Japan) reporting among the highest liver cancer incidence rates worldwide. The remaining 19 cancer registries either had stable rates for both men and women or exhibited differing sex-specific trend patterns from 1993 through 2002.

Factors that may have contributed to the variation in liver cancer incidence trends worldwide include regional differences in the prevalence of risk factors for HCC such

Table 1. Liver cancer incidence rates and male to female rate ratios in select registries, 1998–2002, CI5

Registry/country	Males	Females	Rate ratio	95% CI
France (8 registries)	10.6	2.1	5.0	4.6–5.6
Egypt, Gharbiah[a]	21.9	4.5	4.9	4.2–5.6
Switzerland (2 registries)	7.6	1.7	4.5	3.4–5.9
Singapore: Chinese	21.3	5.0	4.3	3.8–4.8
Slovenia	6.0	1.6	3.8	3.1–4.6
Korea[a]	44.9	12.0	3.7	3.7–3.8
China (2 registries)	27.7	7.8	3.6	3.4–3.7
Australia (5 registries)	4.3	1.3	3.3	3.0–3.6
Germany, Saarland	6.9	2.1	3.3	2.6–4.1
Brazil, Goiania	3.6	1.1	3.3	2.0–5.3
Austria, Tyrol	7.3	2.3	3.2	2.4–4.2
Japan (3 registries)	29.3	9.4	3.1	3.0–3.2
Philippines, Manila	21.8	7.0	3.1	2.8–3.4
Canada (8 registries)	4.2	1.4	3.0	2.8–3.2
Italy (6 registries)	10.9	3.8	2.9	2.7–3.1
U.S.A., SEER (9 registries)	5.9	2.1	2.8	2.7–3.0
Thailand, Chiang Mai	18.4	6.7	2.7	2.4–3.2
Czech Republic	7.1	2.6	2.7	2.5–2.9
New Zealand	4.2	1.6	2.6	2.2–3.1
Slovakia	6.7	2.8	2.4	2.2–2.7
Finland	4.8	2.1	2.3	2.1–2.5
Lithuania	3.8	1.7	2.2	1.9–2.6
India (2 registries)	4.0	1.8	2.2	2.0–2.5
Israel: Jews	3.1	1.4	2.2	1.9–2.6
Sweden	3.0	1.4	2.1	1.9–2.4
Denmark	4.0	1.9	2.1	1.9–2.4
Latvia	4.0	1.9	2.1	1.8–2.5
Estonia	4.2	2.0	2.1	1.6–2.7
Norway	2.1	1.1	1.9	1.6–2.3
Poland (2 registries)	3.0	1.6	1.9	1.5–2.3
U.K., England (5 registries)	3.2	1.8	1.8	1.7–1.9
Costa Rica	5.8	3.8	1.5	1.3–1.8
Uganda, Kyadondo (Kampala)	8.7	5.8	1.5	1.0–2.1
Colombia, Cali	3.1	2.7	1.1	0.9–1.5
Zimbabwe, Harare: African	14.4	12.7	1.1	0.9–1.4
Ecuador, Quito	3.5	3.9	0.9	0.7–1.2

[a]Rates for Korea and Egypt are for 1999–2002.

as HBV and/or HCV infection, dietary aflatoxin exposure, obesity, alcohol-related cirrhosis, and smoking (4, 16, 17). Increasing liver cancer incidence trends in some developed countries such as the United States, the United Kingdom, and Australia may be in part due to increased chronic HCV infection as a result of unscreened blood transfusions and contaminated needles used for medical purposes and with widespread intravenous drug use in previous decades (8, 9, 16, 18); however, the exact contribution of HCV infection to the increasing trends is not well defined. The lag time between HCV infection and the development of HCC is approximately 20 years (19); therefore, the increasing trends throughout the 1980s and 1990s may be related to increased HCV infection that occurred in the 1960s and 1970s. Increases in obesity (20) and by consequence diabetes mellitus may have also contributed to increasing liver cancer incidence rates in some developed regions of the world as both of these factors have been shown to be associated with increased risk for HCC incidence and mortality (21–23). Increases in liver cancer incidence are not only confined to the developed world but have also been observed in less developed regions such as Egypt where rising rates are attributed to extensive HCV transmission from contaminated needles used for parenteral antischistomal therapy between the 1950s and 1980s (24).

In contrast to the increasing liver cancer incidence trends observed mostly in relatively low-risk areas of

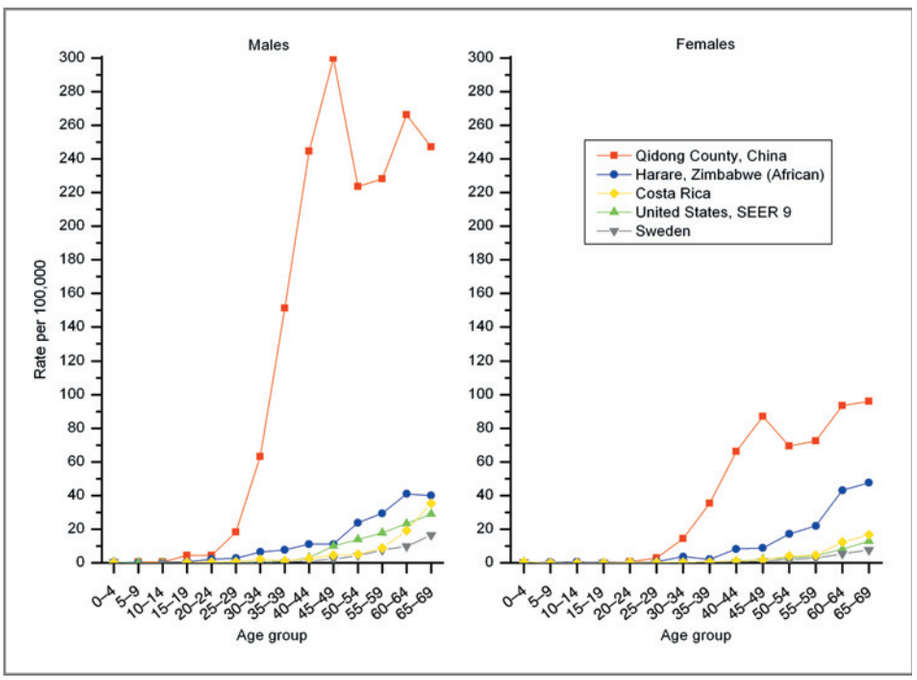

Figure 2. Average annual incidence rates by age group for select registries, 1998–2002. Data for Qidong County, China are for 1993–1997.

North America, Europe, and Oceania, decreasing trends were observed in some high-risk areas of Asia such as Japan, the Philippines, and China. In Japan, HCV is the main risk factor for HCC (25) and significant declines in liver cancer incidence rates in this country have been attributed to reduced transmission of HCV since the 1950s and 1960s as a result of the change in blood bank donation policies from a paid to voluntary system as well as to more stringent legal penalties deterring parenteral amphetamine use, which had increased after the devastation to the country in World War II (10).

Historically, the primary risk factors for liver cancer in China and the Philippines have been HBV infection and dietary aflatoxin exposure (China only), and these 2 factors have been shown to have a synergistic effect on HCC (16). The prevalence of HBV in China and the Philippines is high with more than 8% of the population estimated to have chronic infection with the virus (26). Infant HBV immunization programs have been widely implemented in these 2 countries over the past few decades. Although these programs have led to reductions in HCC incidence among children and adolescents (27–29), they are likely too new to have affected adult liver cancer incidence trends. It is more probable that the observed reduction in the overall liver cancer incidence rates in China could be related to improved sanitary conditions and reduction in consumption of foods contaminated with aflatoxin B1 in over the past decades (7). However, in some more rural areas of China, such as Qidong County, liver cancer incidence rates remain extremely high and do not seem to be declining (12).

In addition to China, Japan, and the Philippines, the European countries of Poland and Sweden have also exhibited decreasing liver cancer trends from 1993 to 2002 for both men and women. The reasons for these decreasing trends are not entirely clear. In Sweden, a decline in autopsy rates in the late 20th century may be related to the decrease in liver cancer incidence in that country, as one study showed that many cases of HCC in Sweden remained undiagnosed prior to autopsy completion upon death (30).

Age-specific liver cancer rates also vary by region within or across countries. The liver cancer incidence rate for men ages 30 to 34 years in Qidong County, China during 1993–1997 was approximately 11 times higher than the rates for men in the same age group in Shanghai and Hong Kong (12), 9 times higher than rates for men in Harare, Zimbabwe, and more than 120 times higher than rates for men in the United States during 1998–2002 (Fig. 2). In China, particularly in rural areas, the majority of HBV carriers acquire the infection at birth. As a result, liver cancer is diagnosed at much younger ages than in other regions of the world, particularly in highly developed areas such as the United States, where HBV and HCV are mainly acquired in adulthood (2). The HBV vaccine is 70% to 95% effective at preventing mother-to-infant HBV transmission when administered within 24 hours of birth (31). Therefore, it is important to broadly apply universal hepatitis B immunization programs in China and worldwide. In contrast, in Africa, a large portion of HBV infection occurs through continuous horizontal transmission beginning in early childhood with very little perinatal infection at birth observed (32). The exact mechanisms of transmission are not fully understood but are thought to be related to the sharing of household items and food (33). The age-specific liver

cancer incidence rate among 45- to 49-year-old men in Qidong County, China is higher than the rates for men in older age groups. This may be related to targeted liver cancer screening practices for high-risk groups (men ages 30–69 years with chronic HBV infection) in Qidong County (34).

High male to female liver cancer incidence rate ratios in some countries may reflect increased prevalence of known risk factors among men. In Egypt, for example, the primary risk factor for liver cancer, hepatitis C viral infection, was widely transmitted by inoculations to control schistosomiasis, which is a disease more common among Egyptian men particularly those in rural areas who acquire it occupationally as farm workers (24). The prevalence of HCV in some areas of Egypt is nearly twice as high in men as in women (35). In contrast, low male to female liver cancer rate ratios in registries such as Quito, Ecuador, Cali (Columbia), Costa Rica, and Harare (Zimbabwe) may indicate similar prevalence of risk factors between the sexes because there are no known susceptibility differences for developing liver cancer by sex (2).

The strength of our study is the use of high-quality cancer registry data from IARC (12). However, IARC incidence data are limited in geographic coverage. Further, registry-specific trends may not be generalized to countries as a whole because data can vary significantly across registries within countries (e.g., China). The interpretation of our findings could also be affected by the accuracy of ICD-10 coding for liver cancer which may vary worldwide with greater accuracy likely in developed countries compared with developing countries. In the United States, the concordance between underlying cause of death and cancer diagnosis for liver cancer using ICD-10 is approximately 76% (36).

In conclusion, liver cancer incidence rates are increasing in several low-risk developed countries in North America, Western Europe, and Oceania. Whereas rates are decreasing in some high-risk countries of Asia, the rates in these countries remain 3 to 4 times higher than those in low-risk areas with increasing rates. Further studies are required to illustrate factors contributing to the divergent liver cancer incidence trends worldwide.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Received July 11, 2011; revised August 24, 2011; accepted August 30, 2011; published OnlineFirst September 15, 2011.

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