Late Age (85 Years or Older) Peak Incidence of Bladder Cancer

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Purpose: We examined the incidence rates of bladder cancer using California Cancer Registry data to determine if any trends exist.

Materials and Methods: Complete records of the 55,159 cases of invasive bladder cancer were examined from the original 92,677 bladder cancer cases recorded in the California Cancer Registry between 1988 and 2004.

Results: California Cancer Registry data showed a universal late age peak in age specific incidence of bladder cancer in men and women, and across ethnic boundaries. The rate of annual increase in the percent of bladder cancer in individuals 85 years or older was increasing about 10 times as rapidly as the percent of the population that was 85 years or older (slope = 0.395 vs 0.0336). Furthermore, during all 17 years the proportion of patients 85 or older with bladder cancer was about twice that of patients with other cancers regardless of gender.

Conclusions: California Cancer Registry data illustrate a peak in the incidence of bladder cancer in individuals 85 years or older. However, to our knowledge there is no known explanation for this late peak in bladder cancer. With the rate of bladder cancer in the population 85 years or older increasing at a rapid pace, it is critical to encourage investigators to include this age group as they continue to search for causative factors and genetic contributors to bladder cancer as well as effective treatments.

Key Words: bladder, bladder neoplasms, elderly, lung neoplasms, age factors

In the United States in 2007 UBC was expected to be responsible for 67,160 new cancer cases and approximately 13,750 deaths.[1] Multiple factors have correlated with UBC, including environmental carcinogens, lifestyle and genetic predisposition.

Industrial exposure to carcinogen has been identified as the major cause of UBC.[2] A study by Brown and Rushton found that industrial exposure to respirable crystalline silica increases the occurrence of UBC, while showing no consistent relationship between exposure and lung cancer.[3] Another study by Kogevinas et al concluded that metal workers, machinists, transport equipment operators and miners were among the major occupational classifications (1 of 10 to 20 UBC cases) with an increased incidence of UBC in men in Western Europe.[4] Findings by Villanueva et al did not prove that ingestion of fluids (tap water and coffee) led to the cancer but strengthened the hypothesis that environmentally influenced carcinogens in such fluids could explain the increase in cancer rates.[5]

Lifestyle factors have also correlated with an increased incidence of UBC. In addition to tobacco, other carcinogens have correlated with UBC. A study by Gan et al determined that diverse exposure to arylamines in nonsmokers is strongly associated with UBC risk and may account for most UBCs.[6] Additionally, a Los Angeles UBC study found that women who used permanent hair dye were at a greater risk for UBC, possibly due to its arylamine content.

The $p27^{Kip1}$ and p53 pathways are believed to be important in UBC occurrence. Rabbani et al studied the prognostic significance of $p27^{Kip1}$ expression in UBC and found that low $p27^{Kip1}$ expression was a significant independent predictor of pelvic recurrence, progression to metastasis, death from disease and death from any cause in patients with UBC.[7]

Additionally, it was concluded by Sanchez-Carbayo et al that the single nucleotide polymorphism SNP309 was frequent in UBC and related to early onset superficial UBC as

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well as T53 mutation status.[8] UBC tumors are known to commonly contain *TP53* mutations and less frequently *HDM2* (a transcriptional target gene of p53) amplifications.

In 1988 cancer was legislated to be a reportable disease in California to create a large sample of cancer data for scientific analysis. The CCR became the repository for the data. We examined CCR UBC related data.

MATERIALS AND METHODS

New cases are reported to the CCR by physicians, health facilities, laboratories, etc, with penalties for failure to report cases. The actual abstracting of cases is done by certified tumor registrars. Ten regional cancer registries act as the first level receiving facility and provide quality assurance, coordination of multiple reports for the same patient and technical help to those reporting cases, and then report the data to the central registry in Sacramento. At this level there is further quality assurance, elimination of duplicate entries, clearance with death certificates and mutual referrals of reports of patients actually residing in other states. CCR is certified by the North American Association of Central Cancer Registries and the entire state is currently part of the National Cancer Institute Surveillance, Epidemiology and End Results Program.

CCR is the population based registry serving the largest population (36 million individuals in 2004) and probably the most diverse in the world. A total of 17 years of data (2,387,316 individual cancers) with all patient, physician and institutional identification removed are available to researchers. This includes 92,677 cases of in situ and invasive UBC from 1988 through 2004. In addition to patient demographics, tumor features are available, such as stage, histology and followup information.

The abstracting process includes a review of reports of tissue examination (surgical pathology, cytology, bone marrow, autopsy, etc). From these reports invasive cancer was separated from in situ cancer and the invasive cases are the basis of this report. All cases were included in 1 or the other of these 2 categories. Since carcinoma in situ can be recognized only on microscopic examination, all of these cases had such an examination. Of invasive cases 97.8% had microscopic examination and the remainder was diagnosed based on clinical examination, radiological procedures, autopsy gross examination, death certificates, etc. Most of the 2.2% of invasive cases without tissue examination were cases located by death certificate clearance only.
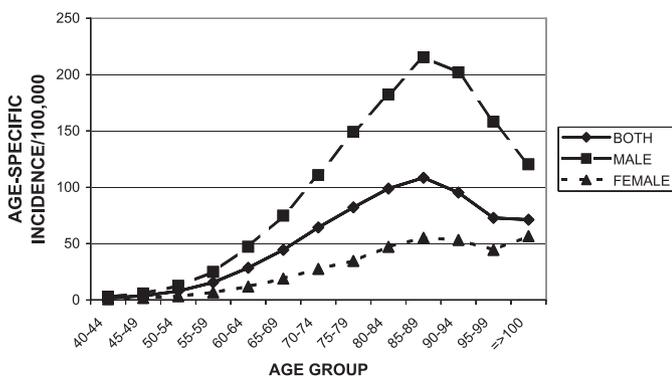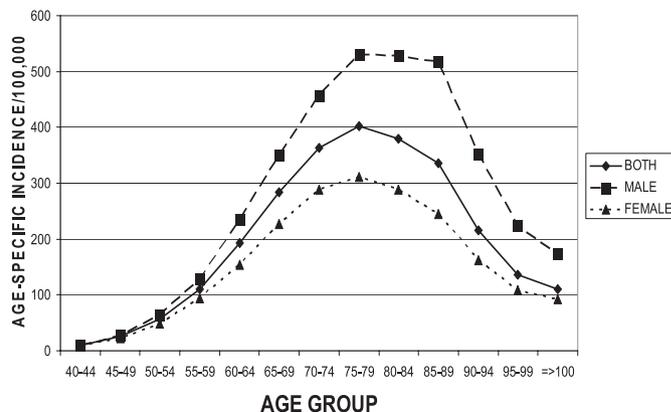

FIG. 2. Age specific incidence rate of all lung/bronchus cancer in 1988 to 2004.

The 55,159 cases of invasive UBC in CCR from 1988 to 2004 form the basis of this report. Of these patients 45,865 (83.2%) were nonHispanic white, 2,231 (4.0%) were black, 4,250 (7.7%) were Hispanic, 2,317 (4.2%) were Asian/Pacific Islander and 517 (0.9%) were of another unknown ethnicity. Additionally, 40,909 of the patients (74.1%) were male and 14,271 (25.9%) were female. A total of 47,871 cases (86.8%) were of the transitional cell type. While age specific and age adjusted rates are calculated for various ethnic, histological and gender groups, only age specific rates were used for this study. Although it peaks slightly younger than invasive UBC, in situ UBC also shows a peak incidence at a later age than most in situ cancers.[9]

Median age for the 2 genders and for all 4 ethnic groups was 67.75 to 71.77 years. While there are statistically significant differences, they are undoubtedly a result of the large numbers used in the sample and they have little practical significance, if any.

RESULTS

CCR data showed a universal peak in the age specific incidence of UBC in men and women 85 years or older with a higher incidence in males (fig. 1). These data differ from those on age specific incidence rates of lung and bronchus cancer, which showed a peak incidence age in the 75 to 79-year-old group (fig. 2). Lung and bronchus data showed a steep decrease in the incidence of lung and bronchus cancer at 85 years or older (fig. 2). Compared to the age specific incidence rates of all invasive cancers a similar trend was followed with a peak age of incidence in the 85 years or older age group (fig. 3). This peak in incidence was further demonstrated by the increasing annual percent of UBC cases in patients 85 years or older (fig. 4). The percent of UBC in individuals older than 85 years increased about 10 times as rapidly as the percent in the population older than 85 years during the 17 years of study (slope = 0.395 vs 0.0336, fig. 4). In contrast, the trend line for the population virtually overlay the line of the population itself.

Figure 5 shows this peak incidence effect seen in all of those 85 years or older across ethnic boundaries. The white population had the highest incidence of UBC with about a third greater the incidence rate of black Americans, which was the group with the next highest incidence population. Additionally, there was a drastic decrease in the UBC inci-
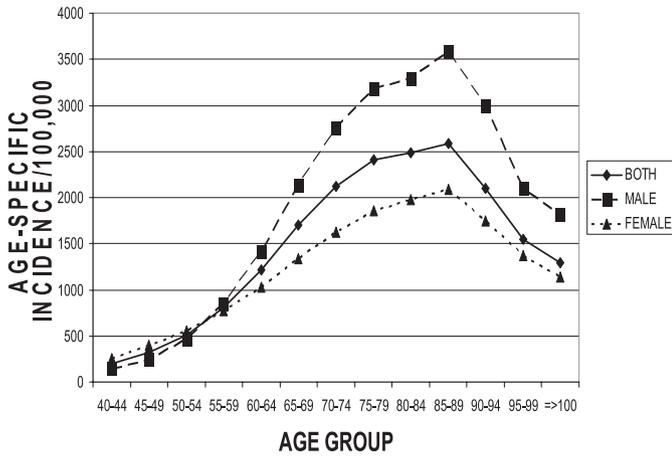

FIG. 1. Effect of gender on UBC incidence

FIG. 3. Age specific incidence rate of all invasive cancer in 1988 to 2004.

FIG. 5. Effect of ethnicity on UBC incidence. *AS/PI*, Asian/Pacific Islander.

dence in all groups at ages 95 to 99 years. Only the rate in the Asian cohort continued to decrease past this age group, while the rate in the other ethnic groups rebounded after that point (fig. 5). The increase in age specific incidence at age 100 years in most groups was believed to be a reflection of the small number in this age group.

Histologically most cases (0.4%) were of the transitional cell type in nature, followed by the epidermoid (squamous cell) type and adenocarcinoma (2.4% and 2.0%, respectively, fig. 6). Transitional cell carcinoma arises in the transitional epithelium lining of the bladder, while adenocarcinoma is assumed to originate in glandular tissue. Epidermoid carcinoma is an aggressive tumor with a poor prognosis and short patient survival. Some groups consider these variants to be dedifferentiated transitional cell carcinoma. In figure 6 magnification of the scale shows that epidermoid carcinoma had the same late peak as transitional cell carcinoma but adenocarcinoma did not, supporting the concept stated.

Finally, the table shows that the proportion of patients with UBC that was 85 years or older was about 10 times that of the total population and about twice that of patients with other cancers regardless of sex. For comparison data on lung/bronchus and prostate cancer are shown.

DISCUSSION

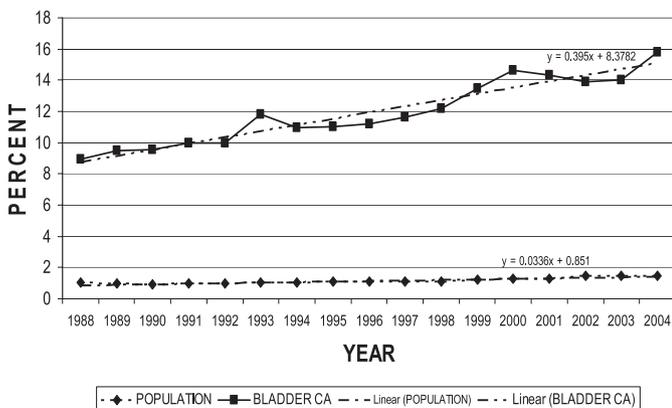Data obtained by CCR were vital in detecting the unique peak incidence of UBC in individuals 85 years or older.[9] This

age is 20 years after the general retirement age and it implies a longer than usual latent period in carcinogenesis. There is a 10-year peak difference between lung/bronchus cancer and UBC (figs. 1 and 2). This is notable since lung cancer and UBC share some of the same carcinogens, that is tobacco and industrial exposure. This disparity could be due to various reasons. The lungs are the first organs to come into contact with the various carcinogens, whereas the bladder receives these carcinogens last and presumably in a more diluted state than the lungs. By the time that they reach the bladder these carcinogens may have lost much of their potency. Hence, the bladder may require longer exposure for the induction of cellular mutations by carcinogens. This would explain the latent peak in UBC in the 85-year-old or older age group, as opposed to that in the lung cancer group, in which carcinogens have direct and full potency contact with the organ (figs. 1 and 2).

We detected no late age peak in the incidence of transitional cell carcinoma of the renal pelvis. This may be due to various reasons, of which one may be that urine in the bladder is more concentrated than in the renal pelvis. This more concentrated urine may be more carcinogenic than the less concentrated urine found in the renal pelvis. These observations warrant further investigation.

Additionally, compared to other causes there is no explanation of why the incidence of UBC has become so high in the 2 genders, but particularly in the female population. While smoking is a common occurrence in each population,
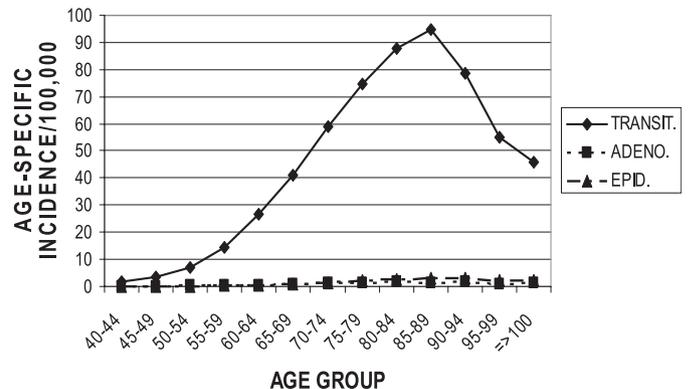

FIG. 4. Percent of individuals 85 years or older vs population. *CA*, cancer.

FIG. 6. Effect of histology on UBC incidence. *TRANSIT.*, transitional cell cancer. *ADENO.*, adenocarcinoma. *EPID.*, epidermoid carcinoma.

Percent of group 85 years or older			
Group	% Women	% Men	% 2 Sexes
Bladder	16.7	10.1	11.8
All invasive Ca except UBC	7.9	5.8	6.9
Total population without Ca	1.6	0.7	1.2
Invasive Ca:			
Lung/bronchus	7.0	5.6	6.2
Prostate	—	5.7	—

work in the industrial sector has traditionally been done by males. An explanation is a possible Rosie the Riveter effect on the female population. The population 85 years or older in 2004 would have been at the youngest born in 1919. During the start of the American involvement in World War II in 1941 women born in 1919 would have been 21 years old. Women of this age during that time worked heavily in the industrial sector to create goods for military and civilian use.[10] A woman who was 21 years old in 1941 would have been 67 years old in 1988 and 93 years old in 2004, making this a reasonable theoretical cohort for study. For the duration of World War II and thereafter women in the age cohort of 85 years or older could well have experienced hazardous industrial working conditions, which may explain the high prevalence in females in this age group. Additionally, inexpensive cigarettes were provided by tobacco companies as well as placed into meal rations (K rations) for the military,[11] further propagating an increase in smoking. Unfortunately because CCR only has data on patients in whom UBC was first diagnosed between 1988 and 2004, it is not possible to do more than speculate on this theory.

If the Rosie the Riveter theory is correct, the subsequent generation (baby boomers) might show a subsequent decrease in the rate of UBC in women. However, this hypothesis may be found to be false due to the increase in the smoking rate in women after World War II and continued industrial exposure.[12] Additionally, it is hypothesized that there will be increased incidence rates of UBC in women of the current working generation due to an increasing number of women serving in the military. These hypotheses require further cohort studies.

Finally, while tobacco use and industrial exposure are known carcinogens involved in lung/bronchus cancer and UBC, to our knowledge it is unknown whether there is a particular carcinogen in the industrial sector that primarily affects the bladder, while having no influence on lung/bronchus cancer. More research on identifying particular carcinogens that affect the transitional epithelium of the bladder is important in the progression of UBC clinical care.

CONCLUSIONS

The percent of patients with UBC who are 85 years or older is increasing with time much more rapidly than that fraction of the population or patients with other cancers. This observed trend has implications for the delivery of medical care and its financing. In addition, it may give new clues to the causes of UBC. Currently to our knowledge there is no published research explaining why the peak incidence of UBC is in the population that is 85 years or older. We know of no clinical trials in participants in the oldest age groups.

Given the increasing rates of UBC in the population 85 years or older, it is critical to encourage investigators to study this age group as they continue to search for causative factors and genetic contributors to UBC as well as develop more effective treatments.

Abbreviations and Acronyms

CCR = California Cancer Registry
UBC = bladder cancer

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EDITORIAL COMMENT

From birth until death the bladder employment agreement requires that it serve as the temporary storage depot for the byproducts of renal purification and detoxification. Occupational exposure and subsequent development of cancer, as first demonstrated in chimney sweeps with scrotal cancer, is a function of the carcinogen, and of the frequency and duration of exposure to the offending substance. Urine, specifically urinary epidermal growth factor, as a promoter of UBC was demonstrated experimentally in the heterotopically transplanted rat bladder model of Momose et al.[1] This arti-

cle lends credence to this hypothesis by its finding of dramatic increases in UBC in individuals whose long life exposed them to prolonged cancer promotion by urine. It is more than likely that the voiding inefficiencies of an aging bladder contribute to an increase in the time of urine contact with uroepithelium.

What, then, is the lesson from this report? As urologists, we should take careful note of the reports of 80-year-old or older patients of changing voiding patterns, investigate their microscopic hematuria with diligence and encourage and participate in studies designed to confirm this report. If further investigation substantiates this health risk, screening for UBC in this population may be of benefit.

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