

Epidemiologic Description of *In situ* Tumors Reported To Cancer Registries, 1995-2005

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Background and Significance

Malignancies are progressive diseases, and when not treated, often lead to death. They can also be invasive, destroying nearby tissue, interfering with organ functions, and characterized by spread (metastasis) of the disease to more distant parts of the body. The earliest stage of disease progression is known as an *in situ* stage, when tumor cells have not penetrated the underlying basement membrane. Without treatment, however, most *in situ* tumors progress to a more advanced stage, whereby the basement membrane is involved and the tumor is described as invasive. *In situ* tumors are generally reportable to a population-based cancer registry so that information on the full spectrum of tumor progression is available. However, these tumors, with the exception of breast cancer *in situ* and bladder cancer *in situ*, are not used in cancer surveillance nor in cancer incidence statistics. The value of collecting reports that are not used should be questioned, particularly in a time of diminishing resources and increasing volume of reports due to the aging of the population.

With the availability of the large data resource from the North American Association of Central Cancer Registries (NAACCR), Cancer in North America (CINA) Deluxe research data set, we evaluate the volume and characteristics of *in situ* cases submitted to population-based central cancer registries in Canada and the U.S. The purpose is to assess the quality and availability of *in situ* cancer data and explore the use of these data for surveillance research.

Methods

The CINA Deluxe 1995-2005 dataset, including both race and Hispanic ethnicity variables, was used for the analysis. The dataset was comprised of NAACCR file submissions

as of December 2007 from registries that gave consent to use their data in the analysis and met the standards for data quality defined by Howe and colleagues [1]. These standards are that data must be available for at least three consecutive years in the 11-year interval, 1995 to 2005. In addition, each included year must meet the following data quality standards: 1) registries' assessment using a standard protocol of the number of duplicate reports is less than 0.1%; 2) submitted data were evaluated for coding accuracy and the reliability is considered error-free on key cancer incidence surveillance variables (e.g., age, sex, race); 3) the category 'unknown' is used to describe age in less than 3% of cases, and race in less than 5% of cases; 4) cases registered with information abstracted from death certificates comprises less than 5% of all cases in each of the diagnosis years; and 5) case ascertainment is at least 90% complete, after adjustment for duplicate reports.

Analysis

We analyzed *in situ* cases to describe the volume of reports and their epidemiologic characteristics, i.e., variation by cancer site [2], year of diagnosis, age, sex, race/ethnicity, U.S. urban/rural location, histology, and affiliation with national cancer surveillance programs (Surveillance Epidemiology and End Results (SEER), National Program of Cancer Registries (NPCR), or the Canadian Registry). In addition, cancer sites with both sufficient numbers of cases (>25) for analysis and a higher than average *in situ* to invasive rate ratio (i.e., for the combined total of all cancer sites for both sexes and all races) were selected and the descriptive characteristics of these site-specific *in situ* tumors were compared with their invasive counterparts by the [descriptive](#)-variables noted above. Rates and counts were suppressed when the category had fewer than 25 cases. Since cervical cancer *in situ* was not a reportable disease for most of the years, 1995-2005, in the study, they were omitted from all analyses. Rates for all sites combined for both invasive and *in situ* rates (and female genital system) do not include them. Tables for all sites combined include malignant systemic tumors (e.g.,

leukemias and lymphomas) but are not listed separately due to the non-existence (by definition) of *in situ* tumors in these sites.

According to the guidelines of the American College of Surgeons (ACOS) Commission on Cancer (COC), cases of VIN III (vulva intra-epithelial neoplasia), VAIN III (vagina intra-epithelial neoplasia), and AIN III (anus intra-epithelial neoplasia) ceased being reportable to hospital tumor registries in January 1996 [3]. As a result, COC hospitals may not collect these cases, which in turn may affect their completeness in the central cancer registry, despite their reportability to the central registry. We also examined the proportions of VIN III, VAIN III, and AIN III cases on the file and compared the results among the states and the national surveillance programs.

Hispanic ethnicity was defined using the NAACCR Hispanic/Latino Identification Algorithm, version 2 (NHIA v2), based on an evaluation of birthplace, race, and/or surname associations with Hispanic ethnicity [4]. The American Indian/Alaska Native category in the race variable was enhanced through linkage with the membership rolls of the Indian Health Service (I.H.S.) for all years of data available on the file.

SEER*Stat was used for the analysis [5]. Statistical significance was determined at a $p < 0.05$ level and confidence intervals for the rates were calculated using the method of Fay and Feuer [6]. All rates were age-adjusted by 5-year age groups and the age-adjusted (AAIR) incidence rates were expressed per 100,000 population at risk, except in the case of very small numbers, per 1,000,000 population at risk. For the sex-specific cancer sites, rates were expressed per 100,000 male or female population. The 2000 US population was used for age standardization [7].

To avoid overlap in the inclusion of registries in both U.S. national programs, and the overlap of metropolitan registries within state registries, the U.S. SEER program was defined by five areas: Iowa, Connecticut, Hawaii, New Mexico, and Utah, as they were in the SEER program for the entire period, 1995-2005. All other U.S. states were defined as part of the U.S.

NPCR program. Since all SEER metropolitan areas overlapped data from their states, they were included in the state data and not separately (i.e., Detroit, Michigan; Atlanta, Georgia; Seattle, Washington; and San Francisco and Los Angeles, California).

Unfortunately, the data from the Canadian Cancer Registry had to be excluded from all analyses, as wide variation by province and cancer site was noted in the inclusion of *in situ* tumors in the dataset. This variation was also apparent in 2004 and 2005 when Collaborative Stage variables were a Canadian national standard. We could not relate any known standard to explain why some provinces had some *in situ* cases throughout the time period, while others did not. Further, some provinces had only breast cancer *in situ* tumors in their case mix. Since the overall proportional volume of *in situ* tumors was vastly different from reports from the US and since we did not have any insight whether it was (1) a reportability issue; (2) a decision by some to omit *in situ* tumors from the data submitted to NAACCR; (3) provincial variability in completeness of reporting these tumors or in reporting standards employed; or (4) something else, we regrettably had to drop these tumors from the analysis.

Data Inclusion

The following table summarizes the U.S. registries included in the analysis [8]. The years of data meeting the data quality criteria are also identified. Only states with data for all years, 1995-2005, were included in trend analysis, due to known bias resulting from analyses with incomplete data for all data years [9].

Alabama, 1998-2005*	Georgia 1998-2005*	Minnesota, 1995-2005	Oregon, 1996-2005*
Alaska, 1996-2005*	Hawaii, 1995-2005	Missouri, 1998-2005*	Pennsylvania, 1995-2005
Arizona, 1995-2004	Idaho, 1995-2005	Montana, 1996-2005*	Rhode Island, 1995-2005
Arkansas, 1997-2005*	Illinois, 1995-2005	Nebraska, 1995-2005	South Carolina, 1997-2005*
California, 1995-2005	Indiana, 1998-2005*	Nevada, 1997-2005*	South Dakota, 2001-2005*
(Includes Los Angeles and Greater Bay Area)	Iowa, 1995-2005	New Hampshire, 1999-2005*	Texas, 1995-2005
Colorado, 1995-2005	Kentucky, 1995-2005	New Jersey, 1995-2005	Utah, 1995-2005
Connecticut, 1995-2005	Louisiana, 1995-2005	New Mexico, 1995-2005	Virginia, 2003-2005*
Delaware, 1995-2005	Maine, 1995-2005	New York, 1995-2005	Washington, 1995-2005
Florida, 1995-2005	Massachusetts, 1997-2005*	North Dakota, 1998-2005*	Wyoming, 1995-2005
	Michigan, 1995-2005	Oklahoma, 1995-2005	

Table 1. U.S. registries with corresponding data years included in the CINA dataset, 1995-2005.

* Registries with missing data years, 1995-2005

Results

Data Quality Issues

The key variable in this project was the designation of a tumor as *in situ* or invasive. The usual method to identify each of these tumors is by the behavior code. However, an *in situ* behavior should be consistent with assignment of an *in situ* code in the stage variable. None of the stage variables is included in the evaluation process for registry certification, however, the stage variables are included in the EDITS metafile for determining “fitness for use” and inclusion in the CINA Deluxe analytic file. So theoretically errors in the dataset should be known to NAACCR. However, if the standard edits metafile does not include a relevant edit, errors can occur in the dataset.

We examined the data set for inconsistencies between assignment of *in situ* behavior and *in situ* stage codes. From 1995 to 2000, no inconsistencies between behavior coding and Summary Stage 1977 coding were found for cases diagnosed. Further, no inconsistencies were found for the 2001-2003 years between the codes in Summary Stage 2000 and behavior. However, inconsistencies were found for 2004-2005 cases, depending on whether *in situ* cases were selected by Derived Stage 2000 or by behavior, and the number of inconsistencies differed based on the selection method. These results are summarized in the data quality report provided to NAACCR. [10] We omitted all cases from the analysis with inconsistent *in situ* behavior and Derived Stage 2000 codes.

In situ Tumors

A total of 836,298 *in situ* tumors were identified, representing 5.8% of the total number (14,425,739) of tumors reported to the registries. Table 2 summarizes the site-specific numbers, rates, and percents of these tumors. The largest numbers and rates of *in situ* tumors occurred for cancer of the breast (male and female, 401,431; AAR 26.07 per 100,000 females only), melanoma (219,612; AAR ~~7.62~~7.62 per 100,000), and colo-rectum (96,642; AAR ~~3.37~~3.37 per

100,000). There were 11 anatomic sites where the rate ratio of *in situ*-to-invasive cases (*100) exceeded the average of 6.14% for all sites combined: floor of the mouth; descending colon; sigmoid colon; rectum; anus, anal canal and ano-rectum (anus); larynx; melanoma of the skin (melanoma); breast; vagina; vulva; and penis.

Table 3 compares the proportional distribution of *in situ* tumors with the invasive tumors by sex, age, race/ethnicity, national program affiliation, urban/rural residence, year of diagnosis, and diagnostic confirmation. Females, persons in five-year age groups from 25-59 years old, white persons, white non-Hispanic persons, and persons residing in the states served by the SEER program had a higher proportion of *in situ* cases than the respective proportion of invasive cases for the same category. Also relatively fewer *in situ* cases than invasive cases were reported in the following categories: children and young adults, aged 0 to 24, black persons, and persons of Hispanic descent. The rates of *in situ* reports were statistically significantly increasing from 1995-2005 at 3.8% per year (based on registries reporting cases for all years), while the trend of the rates of invasive tumors was decreasing, although not significantly, at -0.14% per year. Further, more than 99% of all *in situ* tumors had a positive histologic confirmation, a criterion of the definition and required for the diagnosis of a tumor with an *in situ* behavior.

Site-specific *In situ* Tumors

Tables 4 through 10 describe site-specific *in situ* tumors with sufficient numbers of cases for comparison.

Sex. Table 4 shows that nearly all cancer sites revealed a statistically significant difference in the rate of *in situ* tumors reported between men and women, and in nearly all sites the rate was higher among men. The exception of no statistical difference was found for cancers of the salivary gland, appendix, and pancreas. Statistical higher rates of *in situ* tumors were found in women for cancers of the gallbladder, breast, and thyroid. The rates of *in situ* cases

were higher among women than men for all sites combined due to the magnitude of the breast cancer *in situ* rates in women.

Age. For each cancer site, age groups were compared to the group of 50-74 year old cases (see Table 5). The pattern was similar for most cancers: compared with 50-74 year olds, persons age 0-24 years old had the lowest rate ratio (i.e., a higher rate of *in situ* tumors among 50-74-year-olds than among 0-24-year-olds); 25-49 year olds had a higher rate ratio than the youngest age group, but still lower than the 50-74 year olds, and persons aged 75 and older had a higher rate ratio than 50-74 year olds. This age pattern was statistically significant for most cancers. Exceptions to the pattern were observed when persons, aged 75 years old and older, had a statistically significantly lower rate ratio than the 50-74 year olds (cancers of the floor of the mouth, hypopharynx, anus, breast, corpus uteri and corpus uterus NOS (uterine corpus), vagina, and vulva), or when cases in the 75 years and older group were not statistically different from the 50-74 year olds. This occurred for cancers of the tonsil and ovary.

Race. Table 6 shows that *in situ* cancer rates were higher among white persons than other race groups for all sites combined, and most commonly these differences were statistically significant. Cancers with higher *in situ* rates among the black population were hypopharynx, stomach, small intestine, colon (including many sub-sites of the colon), anus, ~~gallbladder,~~ and lung and bronchus (lung). Higher *in situ* cancer rates among Asian Pacific Islanders (API) occurred for cancers of the stomach, gallbladder and other biliary (i.e., other than liver and intrahepatic bile duct). The exception of no statistical race difference *in situ* cancer rates with the white population was found for cancers of the tonsil, gallbladder, pancreas, larynx (black), ovary (API), vagina (black and AIAN), and prostate (black).

Hispanic Ethnicity. The non-Hispanic white population was more likely to have higher rates of *in situ* tumors than Hispanic persons for all sites combined and for most sites, with the exception of cancers of the stomach, gallbladder, and eye and orbit (eye) where rates were

lower, and vagina, where rates were similar, as shown in Table 7. Further, the rates of *in situ* tumors among the non-Hispanic black population were more similar to Hispanic populations than those for the white population were, with the exception of cancers of the colon, anus, lung, ~~and~~ prostate, and eye.

Metro Area. Residence in metropolitan areas (Table 8) did not distinguish site-specific *in situ* rates from those in non-metropolitan areas to the same extent as other socio-demographic variables. A few cancer sites had *in situ* rates that were higher in the non-metropolitan areas and these were cancers of the lip, rectum, lung, uterine corpus, and prostate. Cancers that were lower in the non-metropolitan areas were those of tongue, esophagus, stomach, and several sub-sites of the colon, anus, gallbladder, larynx, melanoma, breast, and vagina.

National Program. The two national cancer surveillance programs varied somewhat in the site-specific rate ratio of *in situ* tumors (see Table 9). The largest differences, with SEER having a higher rate of *in situ* reports, occurred (choosing an arbitrary minimal 30% difference) for cancers of the lip, melanoma, uterine corpus, ovary, kidney, and eye. The cancer sites where NPCR had the higher rate of *in situ* reports were cancers of the splenic flexure; large intestine, NOS; anus; lung; and prostate.

Histology. Table 10 provides a list of site-specific histologic types of *in situ* tumors. Many *in situ* tumors had histologic types that were specific to *in situ* tumors only. The percentages of non-specified histologic types were higher for *in situ* cases than for invasive cases and these varied by cancer site (e.g., carcinoma *in situ*, not otherwise specified (NOS), with a range of 1.7% for breast cancer to 61% for melanoma). The distribution of histologic types for *in situ* cases was different from invasive cases. For example, for vaginal cancer, the proportion of adenocarcinoma was much lower for *in situ* cases than for invasive cases.

Comparison of *In situ* with Invasive Tumors for Selected Sites

The cancer sites that had higher *in situ*-to-invasive rate ratios than the rate ratio for all cancer sites combined were categorized into three groups (see Table 11). One group of five

cancers occurred in sites with early detection/screening modalities that could affect the rate of *in situ* tumor detection: descending colon, sigmoid colon, rectum, melanoma of the skin, and breast. The second group of four cancers occurred in sites associated with a high risk for HPV infection: anus, vagina, vulva, and penis. Although cancer of the anus could also be grouped with the screening sites, we chose to include them only with the HPV-risk sites. The third group included four sites that we categorized as early awareness sites due to either the visual awareness or otherwise apparent symptomatology associated with interference of normal organ function. These cancers were of the floor of the mouth, larynx, ureter, and eye.

Sex. Table 12 shows the comparison of rate ratios by gender for both *in situ* and malignant tumors of these selected sites. For most sites, males had higher rate ratios within the *in situ* category than the invasive category with the exception of cancer of the anus where it was lower in males, and melanoma and cancer of the larynx, where the rate ratios between the sexes were similar.

Age. Persons aged 75 years old and older, were less likely (had a lower rate ratio) of *in situ* tumors invasive tumors for all cancer screening sites, except melanoma (Table 13). The rate ratios were similar for the other age groups in the screening site category. For the HPV risk sites, the groups of 0 to 24 year olds and 25 to 49 year olds had higher rate ratios of *in situ* tumors than rate ratios of invasive tumors, while persons aged 75 years old and older had lower rate ratios. A different pattern was seen for the early awareness sites: persons 75 years old and older had higher rate ratios of *in situ* tumors than invasive tumors for cancers of the larynx and eye and lower rate ratios for cancers of the floor of the mouth and ureter. The other age groups had similar rate ratios for the two groups of tumors.

Race. The rate ratios of *in situ* tumors in the screening group were somewhat varied based on the individual sites in this category (see table 14). In general, *in situ* rate ratios among black persons and AIAN were lower than the invasive rate ratios, with an exception for cancer of the descending colon where the *in situ* rate ratio was higher than the invasive rate ratio. API

women had a higher rate ratio of breast cancer *in situ* tumors than invasive tumors, while black women had a similar rate ratio and AIAN women had a lower rate ratio. API populations had lower *in situ* rate ratios for all subsites of colon cancers.

The rate ratios for the HPV risk sites were similar between the two groups of tumors for the AIAN population, although cancer of the vulva had a higher *in situ* rate ratio and cancer of the penis had a lower *in situ* rate ratio, characteristics shared with the three other race groups for this cancer site. For cancer of the anus, the black population had a higher rate than the white population and a higher rate ratio than for invasive tumors.

Among early awareness cancer sites, *in situ* rate ratios were lower for the black population and AIAN, although the case counts for specific sites in this group were too small to include in the site-specific analyses. Unlike other sites, the *in situ* rate ratios for cancer of the eye were higher among black and API populations than the invasive rate ratios.

Hispanic Ethnicity. Compared with non-Hispanic white persons, Hispanics had similar rate ratios of *in situ* tumors as they did for invasive tumors in the category of screening sites, as shown in Table 15. However, in the HPV-risk sites, Hispanics had lower rate ratios of *in situ* tumors than invasive tumors relative to the non-Hispanic white population, although the relation did vary by site: Hispanics had a lower *in situ* rate ratios for cancers of the vagina, vulva and penis, and a similar rate ratio for cancer of the anus. Although Hispanics had a similar rate ratio for the group of early awareness sites between the *in situ* and invasive tumors, they had a much higher rate ratio of *in situ* tumors for cancers of the floor of the mouth and eye.

Metro Area. The rate ratio of *in situ* tumors in screening sites was significantly lower in non-metropolitan counties, while no differences were noted in the rate ratios for invasive tumors for the combined group of cancers, as shown in table 16. Lower *in situ* rate ratios occurred for cancer of the breast and melanoma, while they were similar for the colon and rectum cancer sites.

Among HPV risk sites, the overall *in situ* rate ratio was lower in non-metropolitan areas, but the invasive rate ratio was higher in these areas. All site-specific rate ratios were lower for *in situ* tumors than invasive tumors in this group. No metropolitan association was seen in the *in situ* rate ratio for cancer of the penis, nor was an association observed for the invasive rate ratio for cancer of the vagina.

Among the early awareness group of cancers, little metropolitan effect was found for either *in situ* or invasive rate ratios, with the exception of cancer of the larynx, where the *in situ* rate was higher in non-metro areas than metro areas and the invasive rate was higher in non-metro areas than metro areas. The invasive rate ratio for cancer of the eye was significantly higher in non-metropolitan counties, while no difference was found for the *in situ* rate ratios.

National Program. In general, affiliation with one national program or the other did not distinguish the rate ratio of *in situ* tumors from invasive tumors, as shown in table 17. A few exceptions need to be mentioned. NPCR had nearly a 75% higher *in situ* than invasive rate ratio for cancer of the anus than did the SEER program. Cases occurring in NPCR areas had a higher invasive rate ratio for cancers of the larynx and vagina than did the SEER program cases, while the *in situ* rate ratios for the two programs were not different for these sites. Conversely, NPCR areas had lower *in situ* rate ratios for melanoma, and cancers of the breast, vulva, ureter, and eye when the program invasive rate ratios were not different.

Reports of Intra-epithelial Tumors

Although ACoS COC has not required reporting of VIN III, VAIN III, and AIN III cases since January 1996, some registries continued to receive reports. The state and annual variability in the volume of these reports suggest that the data are at best incomplete, but also likely to be inconsistent across registries. VIN III and VAIN III reports had consistent annual case counts from 1995 through 2005. The numbers of AIN III were larger, with most cases reported since 2001 in California, Washington, Pennsylvania, Colorado and Florida, while

Georgia and Massachusetts had a surge of reports in 2004 and 2005 compared with their previous years. Michigan had an increase in their annual count of AIN III beginning in 2000.

Discussion

In this descriptive exploration of *in situ* tumors reported to cancer registries, the pattern of *in situ* tumors, and their descriptive characteristics, generally follows that of invasive tumors: higher rates in invasive tumors would predict higher rates for *in situ* tumors. The most notable exception would be the higher *in situ* rates in women primarily attributable to the high rates of breast cancer *in situ* reports in women.

Further the lower *in situ* rates non-white populations and in children, young adults, and the elderly may be related to the specific cancer types that occur in these groups, in other words the cancer types most common in these categories are not the cancers that can occur (e.g., leukemia in children) or do occur (e.g., prostate cancer) in an *in situ* stage. Some of the differences in the two national surveillance program could be attributable to data quality issues (e.g., the rates of prostate cancer *in situ* or large intestine NOS), more thorough case ascertainment (melanoma), or in differences in the underlying risks and cancer profiles in the two programs.

The rate of *in situ* tumors in cancer sites with screening opportunities are higher than the *in situ* rate for all cancers and this would appear to reflect that these modalities do detect disease at the earliest time of disease progression. The higher rate of *in situ* disease in cancer sites associated with HPV-risk may reflect the impact of close medical surveillance of high-risk populations that results in earlier detection of cancers.

We found that the standard quality assurance programs used by cancer registries did not include a sufficient evaluation tools to result in the highest quality information [10]. However, feedback to the standard-setters has resulted into a modification of these tools so that the errors

found in this study will be able to be rectified at the reporting source. Future investigators should be able to get a clean data set for study.

This paper started with the question of the value of collecting *in situ* reports. At nearly 6% of all reports received by cancer registries, this is not trivial. Cancer sites with both sufficient numbers of cases (>25) for analysis and a higher than average *in situ* to invasive rate ratio accounted for 91% of all *in situ* cases. However, the value of a population-based registry with a census of all tumors is that unlike hypothesis driven registers, the census enables investigators to be immediately responsive to the advent and adoption of early detection modalities; to changes in cancer risk and exposures; and to emerging trends or disparities in cancer surveillance statistics in specific population groups.

Breast cancer *in situ* has only recently been reported in surveillance statistics as it has been shown to be highly associated with the penetration levels in the population at risk of mammography screening: the more screening the higher the breast cancer *in situ* rates [11]. HPV risk was not of population concern 30 years ago when many registries were established, but the census of reports with all phases of tumor progression enables some insights into changes in the incidence of these conditions. Of course, this is tempered by the change in reporting criteria by the COC affecting hospital collection of these tumors. However, in general, unforeseen changes in risk, exposure, early detection and other factors can be identified through surveillance of malignant tumors across the disease progression. Of course, the data could be more widely and routinely used for this purpose to enhance the richness of the census of registry information.

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