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Frequency and distribution of cancers among gender minority patients: an analysis of U.S. national surveillance data

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Abstract

Background—Transgender people and persons with disorders of sex development (DSD) are two separate categories of gender minorities, each characterized by unique cancer risk factors. Although cancer registry data typically include only two categories of sex, registrars have the option of indicating that a patient is transgender or has a DSD.

Methods—Data for primary cancer cases in 46 states and the District of Columbia were obtained from the North American Association of Central Cancer Registries (NAACCR) database for the period 1995–2013. The distributions of primary sites and categories of cancers with shared risk factors were examined separately for transgender and DSD patients and compared to the corresponding distributions observed in male and female cancer patients. Proportional incidence ratios were calculated by dividing the number of observed cases by the number of expected cases. Expected cases were calculated based on the age- and year of diagnosis-specific proportions of cases for each cancer category observed among male and female patients.

Results—Transgender patients have significantly elevated proportional incidence ratios (95% confidence intervals) for viral infection induced cancers compared to either males (2.3; 2.0–2.7) or

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Authorship contribution statement

RN, KW, MG contributed to study concept, study design and data acquisition.
RN conducted data analysis and put together data tables.
RN and MG prepared the original draft of the manuscript.
RN, KW, AJ, DS, VT, MG provided critical review of the manuscript for important intellectual content.
RN, KW, AJ, DS, VT, MG approved the final version of the manuscript.

Conflict of Interest Statement

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females (3.3; 2.8–3.7). Adult DSD patients have a similar distribution of cancer sites compared to male or female patients but DSD children have ten times more cases of testicular cancer than expected (95% confidence interval: 4.7–20).

Conclusion—The proportions of certain primary sites and categories of malignancies among transgender and DSD cancer patients are different from the proportions observed for male or female patients.

Keywords

cancer; transgender persons; disorders of sex development; epidemiology

1. INTRODUCTION

Population-based cancer registries are important in assessing trends in cancer frequency, distribution, and survival [1]. Although reports using registry data typically include only two categories of sex, some groups of people cannot be explicitly categorized as “male” or “female”. Transgender people and persons with disorders of sex development (DSD) represent two distinct groups with unique medical treatments and cancer risk factors [2].

Transgender people comprise a diverse group of individuals whose biological sex does not match their gender identity [3]. Typically, gender is assigned at birth based on the external appearance of the genitalia, whereas gender identity is one’s sense of being a boy/man, girl/woman, neither or both [4]. Although cancer risk in this population is not well understood, it remains an important area of concern [5, 6] because transgender people have higher prevalence of established cancer risk factors such as sexually transmitted infections and lack of screening [7]. In addition, transgender people who undergo gender affirmation treatment may receive high doses of sex steroid hormones for extended periods of time; the carcinogenicity of hormone therapy in this context is also unclear [8, 9].

The term DSD refers to a heterogeneous group of conditions affecting the development of sex chromosomes, gonads, or anatomic sex [10, 11]. DSD can be identified at birth by the presence of atypical genitalia, during adolescence because of absence of or contra-sexual pubertal development, or in adulthood by fertility problems. Patients with DSD may be at higher risk for gonadal malignancies depending on the specific condition [12–14]. For example, DSD patients who have Y chromosome material may have an increased risk of germ cell tumors [15–17].

Transgender people and persons with DSD are often included in the broad and heterogeneous category of sexual and gender minorities. Sexual minorities are defined as individuals who identify as lesbian, gay, or bisexual or report same-sex attraction or same-sex behavior [18]. By contrast, transgender people and persons with DSD are usually described as gender minorities, although an argument can be made that DSD may or may not belong in this group [2].

Data on cancer cases in all 50 states and the District of Columbia are collected by the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and

End Results (SEER) program of the National Cancer Institute. These data are compiled by the North American Association of Central Cancer Registries (NAACCR); access to the NAACCR database offers opportunities for analyses of cancer patterns and trends within the entire United States population [19]. In collecting information for the variable 'sex', registrars have always had the option of selecting one of the mutually exclusive categories of "male," "female," "transsexual" and "other (hermaphrodite)," based on information in the medical records, which may be self-reported or indicated by a healthcare provider [20]. Although inaccurate, the term 'hermaphrodite' has historically been used to refer to people with DSD [21].

To-date these data have not been examined on a national scale. For this reason, the objectives of this study were to examine the distributions of primary sites and categories of malignancies among transgender and DSD cancer patients reported to NAACCR and compare these distributions to those observed among patients characterized as "male" or "female."

2. METHODS

Demographic and tumor information for all first primary cancer cases diagnosed from 1995 through 2013 was extracted from the NAACCR Cancer in North America (CiNA) Deluxe database for the 46 participating states and the District of Columbia for all years with available data [22]. As categories of gender beyond male and female are not traditionally released with CiNA data, a consent process was required from each individual state for access to the full set of codes for the variable "sex". Four states did not provide consent to use these data and were not included in analyses. Gender was categorized as male, female, transgender, or DSD based on the NAACCR variable "sex."

Patients were also characterized by year of diagnosis, age at diagnosis, race/ethnicity, region of diagnosis, insurance status, and primary site of cancer. Year of diagnosis was categorized into 5-year groups, age was categorized into 10-year groups, and region of diagnosis was categorized according to the U.S. Census Bureau designation as: Northeast (CT, ME, MA, NH, RI, NJ, NY, PA), Midwest (IN, MI, OH, WI, IA, MO, NE, ND, SD), South (DE, D.C., FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX), and West (AZ, CO, ID, NM, MT, UT, NV, WY, AK, CA, HI, OR, WA).

To compare the distributions of cancer sites and categories of malignancies among transgender and DSD patients to that observed among male and female patients, the proportional incidence ratios (PIR) and corresponding 95% Poisson confidence intervals (95% CI) were calculated for the primary sites with greater than five cases and for groups of cancers with shared risk factors. Cancers were grouped as any viral infection induced cancers, AIDS-defining cancers, HPV-related cancers, and smoking-related cancers. PIR was calculated by dividing the number of observed cases by the number of expected cases. Expected cases were calculated based on the proportion of cases for each primary site or category among all cancers reported for males and females, separately, within age- and year of diagnosis- specific strata. PIR was restricted to patients ≥20 years old at diagnosis, except for testicular cancers in DSD patients because of the reported increased risk of pediatric

germ cell tumors in this group [23]. In this case, PIR was calculated separately for patients 0–19 years old within 10-year age- and year of diagnosis- specific strata. Statistical analysis was conducted using SAS 9.4.

3. RESULTS

A total of 1,223 cases diagnosed between 1995 and 2013 in the NAACCR database had a value for the “sex” variable other than “male” or “female.” Two-thirds (n=805) were transgender and one-third (n=418) were DSD patients (Table 1). A total of 21,824,591 primary cancer cases diagnosed in the U.S. during the same period were characterized as either “male” or “female.” The number of patients recorded as either transgender or DSD increased over time and was greatest in the most recent time period (2010–2013). This secular trend was not observed for male or female patients. Compared to male and female patients, transgender and DSD patients were more likely to be diagnosed at younger ages. A greater proportion of the DSD patients were diagnosed as children or adolescents than transgender patients (2.6% vs. 0.7%) and the percentage of DSD patients younger than 30 years old at diagnosis was nearly double the corresponding percentage of male and female referents; however the majority of DSD cancer patients were diagnosed at more advanced age. The race/ethnicity distributions were similar for males and females, but transgender and DSD patients included greater proportions of minorities (29–30%). Similar to male and female patients, the greatest proportion of DSD patients was located in the south. However, transgender patients were more likely to be located in the West (41%). Transgender patients were also more likely to be Medicaid-insured or uninsured, while nearly one-third of DSD patients had Medicare.

The frequencies and distributions of primary cancer sites among adult transgender patients are presented in Table 2. The most common cancer sites were lung/bronchus (95 cases), colorectum (86 cases), non-Hodgkin lymphoma (65 cases), prostate (48 cases), and breast (43 cases). The highest PIRs were observed for anal (9.5; 95% CI: 6.6–13) and breast (21; 15–28) cancers compared to males, anal (9.5; 6.7–13) and base of tongue/tonsillar (7.6; 4.4–12) cancers compared to females, and Kaposi sarcoma compared to either sex (vs. males: 9.2; 6.6–13; vs. females 236; 169–320). Significantly lower PIRs were observed for melanoma (0.5; 0.4–0.8), prostate (0.3; 0.2–0.4), and testicular (0.3; 0.1–0.6) cancers compared to males, and breast (0.2; 0.1–0.2), cervical (0.3; 0.1–0.6), ovarian (0.4; 0.2–0.8), and thyroid (0.3; 0.2–0.5) cancers compared to females.

Table 3 presents the frequency and PIR (95% CI) results for DSD patients. One-quarter of the cases (n=101) were cancers of the breast. The other most common sites were colorectum (48 cases), lung/bronchus (48 cases), melanoma (28 cases), and prostate (19 cases). A significantly elevated PIR among DSD patients was observed for breast cancer (101; 82–123) compared to males. The PIR for testicular cancer comparing DSD adults to adult males was not elevated; however, the corresponding PIR for DSD children 0–19 years of age was significantly higher than expected (10; 4.7–20). The majority (82%) of childhood cancers in DSD patients were found in the testis. Significantly lower PIRs were observed for prostate (0.2; 0.1–0.3) and urinary bladder (0.4; 0.2–0.8) cancers compared to males and

endometrium (0.4; 0.2–0.8), ovarian (0.4; 0.1–0.9), and thyroid (0.4; 0.2–0.9) cancers compared to females.

The results for the PIRs for the grouped cancers with shared risk factors are presented in Table 4. Transgender patients had significantly elevated PIRs for viral infection induced cancers, compared to either males or females, but had similar incidence of smoking related cancers. The PIRs were greatest for HPV infection induced cancers compared to males (PIR=3.2, 95% CI: 2.4–4.0) and any viral infection related cancers compared to females (PIR=3.3, 95% CI: 2.8–3.7). The distribution of the categories of malignancies with shared risk factors among DSD patients did not differ from the distributions observed among male or female patients.

4. DISCUSSION

In this analysis of nationwide population-based cancer surveillance data, the distributions of primary sites and categories of malignancies in transgender and DSD cancer patients differed from the distributions observed in male and female patients. Notably, we observed higher than expected numbers of viral infection related cancers in adult transgender patients and a greater than expected proportion of testicular cancer in DSD children.

Most information on cancer in transgender and DSD patients is found in case reports and a few small studies conducted at specialized gender clinics. For this reason, comparisons to previous reports are somewhat limited and may not be appropriate, given the population-based nature of the present analysis.

One previous population-based report for transgender cancer patients diagnosed in the SEER region between 1978 and 2013 also found greater than expected numbers of infection-induced cancers such as anal and base of tongue/tonsillar cancers as well as Kaposi sarcoma and non-Hodgkin’s lymphoma and fewer than expected numbers of melanoma cases [7]. No DSD cancer patients were included in that analysis. SEER data covers only approximately 28% of the United States [24] and although the SEER report included a wider range of diagnosis years, only 354 transgender patients were identified, compared to the over 800 transgender patients found with the expanded coverage of NAACCR data.

While population-based reports such as the SEER report and the current analysis are useful for understanding how the distribution of cancer site differs between transgender and non-transgender populations, conclusions about differences in risk cannot be determined without longitudinal studies of sufficient size. A distinguishing feature of a longitudinal study compared to a proportional incidence study such as ours is the ability to ascertain incident cases in a well-defined population at risk followed over time. A recent example of such longitudinal study is the analysis of electronic medical record data on transmasculine and transfeminine patients enrolled in Kaiser Permanente health plans [25]. The results of that cohort study demonstrated higher incidence of viral infection related cancers for transgender patients compared to reference males but not females. The authors also reported lower incidence of prostate cancer among transfeminine cohort members compared to reference males.

Evaluation of cancer risk among DSD patients is more challenging because the broad category of DSD represents multitude of diverse conditions. Most previous studies of cancer risk among DSD patients have focused on gonadal malignancies. The increase in risk and the timing of tumor development in this population are not well understood and vary depending on the specific condition and presence of Y chromosome material. Prophylactic gonadectomy is often recommended because of this uncertainty [26, 27].

This study represents the largest, population-based analysis of transgender and DSD cancer patients to date. The most notable limitation of these data is the lack of information on population denominators, which precluded proper evaluation of disease risk. Although the precise prevalence of DSD and gender nonconformity in the United States is a matter of ongoing research [28], available data indicate that taken together these groups may represent a population of considerable size. It is estimated that approximately 0.6% of US adults may be identifying as transgender or gender nonconforming [29]. Similarly, infants with DSD may represent as many as 1.7% of all live births [30]. As cancer registries already collect data on other subpopulations, a systematic ascertainment of new cases among transgender and DSD persons appears well justified, and will undoubtedly increase our understanding of cancer incidence and prognosis in these population groups.

Other limitations of the NAACCR data include lack of information on sex assigned at birth for transgender patients, specific underlying condition for DSD patients, and history of relevant treatments such as hormone therapy or surgery. For example, 5% of cases observed among transgender patients were breast cancers; however, it was impossible to determine if these occurred in natal men or natal women. In the case of DSD patients, without information on specific condition we were unable to determine if patients are phenotypically or genetically male or female. For example, patients with XY gonadal dysgenesis appear phenotypically female but are genetically male. These limitations notwithstanding, the present analysis demonstrates that the patterns of cancer diagnoses among transgender and DSD patients may be quite different from those observed in male and female cancer patients. These data also demonstrate that the on-going efforts to implement more systematic documentation of sex assigned at birth and gender identity in the medical records [31] will provide important opportunities for future analyses of cancer registry data. The gender categories in registry databases and efforts to accurately capture cases among gender minorities should be expanded, as these populations clearly have different cancer risks than the general population. This effort has already started with the recent inclusion of additional ‘sex’ variable options of “transsexual, natal male” and “transsexual, natal female” in the NAACCR database. The description of the “other” category has also been modified to more accurately describe DSD patients as “other (intersex, disorders of sexual development/ DSD)” [32]. In the shorter term, the registry data may allow examination of prognostic factors and determinants of survival among transgender and DSD cancer patients. Once denominator data on these populations become available, a variety of analyses assessing cancer risk and risk factors will be possible.

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Highlights

- Cancer registrars can indicate if a patient is a gender minority
- To-date, nationwide data on cancer in gender minorities has not been examined
- Proportion of viral-infection induced cancers is greater in transgender patients
- Children with DSD have greater than expected numbers of testicular cancer

Table 1

Demographic characteristics of patients with a first primary cancer diagnosed 1995–2013 in the United States and reported to NAACCR

	Categories of NAACCR variable 'sex'			
Patient Characteristics	**All males n (%)**	**All females n (%)**	**Transgender* n (%)**	**DSD* n (%)**
Year of Diagnosis				
1995–1999	2,234,226 (20.5)	2,222,119 (20.3)	89 (11)	64 (15)
2000–2004	2,873,581 (26.4)	2,831,056 (25.9)	160 (20)	93 (22)
2005–2009	3,211,494 (29.5)	3,199,436 (29.3)	240 (30)	125 (30)
2010–2013	2,576,699 (23.6)	2,675,980 (24.5)	316 (39)	136 (33)
Age at Diagnosis				
0–19 years	129,890 (1.2)	115,661 (1.1)	6 (0.7)	11 (2.6)
20–29 years	143,135 (1.3)	192,809 (1.8)	26 (3.2)	11 (2.6)
30–39 years	288,041 (2.6)	541,462 (5.0)	94 (12)	31 (7.4)
40–49 years	781,196 (7.2)	1,397,356 (12.8)	159 (20)	40 (9.6)
50–59 years	2,087,488 (19.2)	2,131,818 (19.5)	228 (28)	60 (14)
60–69 years	3,171,348 (29.1)	2,415,296 (22.1)	173 (21)	105 (25)
70+ years	4,294,902 (39.4)	4,134,189 (37.8)	119 (15)	160 (38)
Race/Ethnicity				
Non-Hispanic White	8,605,673 (79.0)	8,585,841 (78.6)	556 (69)	279 (67)
Non-Hispanic Black	1,119,580 (10.3)	1,081,059 (9.9)	113 (14)	55 (13)
Non-Hispanic Other	301,540 (2.8)	368,350 (3.4)	32 (4.0)	18 (4.3)
Hispanic	705,930 (6.5)	775,659 (7.1)	91 (11)	51 (12)
Unknown	163,277 (1.5)	117,682 (1.1)	13 (1.6)	15 (3.6)
Region of Diagnosis				
Northeast	2,482,938 (22.8)	2,607,939 (23.9)	173 (21)	24 (5.7)
Midwest	1,870,688 (17.2)	1,894,997 (17.3)	105 (13)	66 (16)
South	4,099,627 (37.6)	3,972,592 (36.4)	200 (25)	229 (55)
West	2,442,747 (22.4)	2,453,063 (22.4)	327 (41)	99 (24)
Primary Payer at Diagnosis				
Private Insurance	1,944,272 (17.8)	2,263,025 (20.7)	146 (18)	98 (23)
Medicaid	398,232 (3.7)	476,530 (4.4)	118 (15)	28 (6.7)
Medicare	2,860,340 (26.3)	2,747,714 (25.1)	148 (18)	131 (31)
Other	917,703 (8.4)	816,025 (7.5)	65 (8.1)	26 (6.2)
Not Insured	278,942 (2.6)	267,344 (2.4)	52 (6.5)	11 (2.6)
Unknown	4,496,511 (41.3)	4,357,953 (39.9)	276 (34)	124 (30)
TOTAL	10,896,000	10,928,591	805	418

DSD=disorders of sex development

*NAACCR values of "transsexual" and "other (hermaphrodite)" are referred to here as transgender and DSD, respectively.

Table 2

Distribution of primary site among adult transgender patients and site-specific proportional incidence ratios (PIR) compared to males and females in the NAACCR database within year- and age- specific strata.

Site of primary cancer	Transgender n (%)	PIR (95% CI) Compared to all males	PIR (95% CI) Compared to all females
Anus	35 (4.4)	9.5 (6.6, 13.2)	9.5 (6.7, 13.3)
Base of tongue/tonsil	17 (2.1)	1.4 (0.8, 2.2)	7.6 (4.4, 12.2)
Breast	43 (5.4)	20.7 (15.0, 27.9)	0.2 (0.1, 0.2)
CNS/Brain	19 (2.4)	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)
Cervix	6 (0.8)	NE	0.3 (0.1, 0.6)
Colorectum	86 (11)	1.1 (0.9, 1.4)	1.5 (1.2, 1.8)
Endometrium	10 (1.3)	NE	0.2 (0.1, 0.4)
Esophogus	9 (1.1)	0.8 (0.4, 1.5)	3.6 (1.7, 6.9)
Hematopoietic	36 (4.5)	1.1 (0.8, 1.5)	1.7 (1.2, 2.4)
Hodgkin lymphoma	18 (2.3)	1.7 (1.0, 2.7)	3.2 (1.9, 5.0)
Kaposi Sarcoma	41 (5.1)	9.2 (6.6, 12.5)	235.9 (169.3, 320.1)
Kidney and renal pelvis	21 (2.6)	0.6 (0.4, 1.0)	1.26 (0.8, 1.9)
Larynx	8 (1.0)	0.8 (0.3, 1.5)	3.0 (1.3, 5.9)
Liver/bile duct	27 (3.4)	1.5 (1.0, 2.2)	5.1 (3.4, 7.4)
Lung and bronchus	95 (12)	1.1 (0.9, 1.3)	1.4 (1.1, 1.7)
Melanoma	33 (4.1)	0.5 (0.4, 0.8)	0.7 (0.5, 1.0)
Non-Hodgkin lymphoma	65 (8.1)	1.7 (1.3, 2.1)	2.7 (2.0, 3.4)
Ovary	9 (1.1)	NE	0.4 (0.2, 0.8)
Pancreas	19 (2.4)	1.1 (0.7, 1.8)	1.4 (0.8, 2.2)
Pituitary gland	13 (1.6)	2.0 (1.0, 3.4)	1.9 (1.0, 3.3)
Prostate gland	48 (6.0)	0.3 (0.2, 0.4)	NE
Stomach	11 (1.4)	0.8 (0.4, 1.5)	1.6 (0.8, 2.9)
Testis	8 (1.0)	0.3 (0.1, 0.6)	NE
Thyroid	12 (1.5)	0.7 (0.4, 1.3)	0.3 (0.2, 0.5)
Urinary bladder	26 (3.3)	0.7 (0.5, 1.1)	2.3 (1.5, 3.4)
Vagina	7 (0.9)	NE	6.4 (2.6, 13.1)

NE=No Expected; no expected cases due to sex-specific cancer site.

Table 3

Distribution of primary site among DSD patients and site-specific proportional incidence ratios (PIR) compared to males and females in the NAACCR database within year- and age- specific strata.

Site of primary cancer	DSD n (%)	PIR (95% CI) Compared to all males	PIR (95% CI) Compared to all females
Breast	101 (25)	101.0 (82.3, 122.8)	0.8 (0.7, 1.0)
CNS/Brain	12 (2.9)	1.0 (0.5, 1.8)	0.9 (0.5, 1.5)
Cervix	9 (2.2)	NE	1.1 (0.5, 2.0)
Colorectum	48 (12)	1.2 (0.9, 1.6)	1.3 (0.9, 1.7)
Endometrium	8 (2.0)	NE	0.4 (0.2, 0.8)
Hematopoietic	14 (3.4)	0.8 (0.4, 1.3)	1.0 (0.5, 1.7)
Kidney and renal pelvis	12 (2.9)	0.9 (0.4, 1.5)	1.4 (0.7, 2.4)
Lung and bronchus	48 (12)	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)
Melanoma	28 (6.9)	1.1 (0.7, 1.5)	1.4 (0.9, 2.0)
Non-Hodgkin lymphoma	17 (4.2)	1.0 (0.6, 1.6)	1.2 (0.7, 1.9)
Prostate gland	19 (4.7)	0.2 (0.1, 0.3)	NE
Stomach	8 (2.0)	1.2 (0.5, 2.3)	1.8 (0.8, 3.6)
Thyroid	6 (1.5)	1.1 (0.4, 2.4)	0.4 (0.2, 0.9)
Testis in childhood *	9 (82)	10.3 (4.7, 19.5)	NE
Testis in adulthood **	10 (2.2)	1.1 (0.5, 2.1)	NE
Urinary bladder	10 (2.5)	0.4 (0.2, 0.8)	1.2 (0.6, 2.3)

NE=No Expected; no expected cases due to sex-specific cancer site.

* Represents frequency and percent of any testicular cancer among total cancers in DSD patients 0–19 years at diagnosis; PIR (95% CI) restricted to patients 0–19 years of age at diagnosis.

** Includes undescended testis (90% of the cases)

Table 4

Proportional incidence ratios comparing adult transgender and DSD patients to male and female patients in the NAACCR database for categories of cancers with shared risk factors within year- and age- specific strata.

	Transgender patients			DSD patients		
Category of cancer with shared risk factors	**n (%)**	**PIR (95% CI) Compared to all males**	**PIR (95% CI) Compared to all females**	**n (%)**	**PIR (95% CI) Compared to all males**	**PIR (95% CI) Compared to all females**
Any viral infection related cancers*	214 (27)	2.3 (2.0, 2.7)	3.3 (2.8, 3.7)	37 (9.1)	1.0 (0.7, 1.4)	1.2 (0.8, 1.6)
AIDS-defining cancers**	112 (14)	2.6 (2.1, 3.1)	2.3 (1.9, 2.8)	26 (6.4)	1.4 (0.9, 2.0)	1.1 (0.7, 1.7)
HPV infection induced cancers§	63 (7.9)	3.2 (2.4, 4.0)	2.1 (1.6, 2.7)	13 (3.2)	1.8 (0.9, 3.0)	1.1 (0.6, 1.9)
Smoking related cancers^	202 (25)	0.9 (0.8, 1.0)	1.3 (1.1, 1.5)	97 (24)	0.8 (0.6, 1.0)	1.0 (0.8, 1.3)

*Includes cancers of the anus, base of tongue/tonsil, cervix, liver/bile duct, oropharynx/hypopharynx/pharynx, and lymphomas (Hodgkin and non-Hodgkin) and Kaposi sarcoma

**Includes cervical cancer, Kaposi sarcoma, and non-Hodgkin lymphoma

§Includes cancers of the anus, base of tongue/tonsil, cervix, and oropharynx/hypopharynx/pharynx

^Includes cancers of the cervix, esophagus, head/neck, kidney, larynx, lung, pancreas, stomach, trachea, and bladder