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Small Intestinal Cancer: a Population-Based Study of Incidence and Survival Patterns in the United States, 1992 to 2006

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Abstract

Background: The etiology of cancers of the small intestine is largely unknown. To gain insight into these rare malignancies, we evaluated contemporaneous incidence and survival patterns.

Methods: Using small intestine cancer data from 12 population-based registries of the Surveillance, Epidemiology and End Results Program, we calculated age-adjusted and age-specific incidence rates (IRs), IR ratios, and relative survival (RS) rates.

Results: In total, 10,945 small intestine cancers (IR = 2.10/100,000 person-years) were diagnosed during 1992 to 2006, including carcinomas (n = 3,412; IR = 0.66), neuroendocrine cancers (n = 4,315; IR = 0.83), sarcomas (n = 1,084; IR = 0.20), and lymphomas (n = 2,023, IR = 0.38). For all histologic groups, males had significantly higher IRs than females, and distinct age-specific gender patterns were limited to intermediate-/high-grade lymphomas. Neuroendocrine cancer rates varied significantly by race, with rates highest among blacks and lowest among Asians/Pacific Islanders. Carcinoma IRs were highest among blacks; sarcoma IRs were highest among Asians/Pacific Islanders; and lymphoma IRs were highest among whites. Age-specific IR patterns were similar across racial/ethnic groups. During 1992 to 2006, duodenal cancer IRs increased more markedly than those for other subsites. RS varied little by gender or race. Neuroendocrine cancers had the most favorable RS, and carcinomas had the least favorable. The greatest improvement in 5-year RS from 1992 to 1998 to 1999 to 2005 was observed for sarcomas and lymphomas.

Conclusions: Distinct small intestine cancer IR patterns according to histologic subtype suggest different underlying etiologies and/or disease biology, with susceptibility varying by gender, racial/ethnic groups, and subsite. Temporal patterns support a possible role for diagnostic bias of duodenal cancers.

Impact: Future epidemiologic studies of small intestine cancer should consider histologic subtype by gender, race/ethnicity, and subsite. *Cancer Epidemiol Biomarkers Prev; 19(8); 1908–18. ©2010 AACR.*

Introduction

The small intestine comprises 98% of the intestinal surface and 90% of the length of the bowel, yet it is a rare site of malignancy compared with the much shorter colon (1). Although small intestinal and colonic malignancies are thought to share some risk factors, including inflammation and genetic susceptibility (2-4), differences in microbial flora, metabolism of bile acids, and intestinal transit time are postulated to account for some of the variation in incidence rates (IR) between small and large bowel cancers (4). Despite some clues, the etiology of small intestinal cancers remains largely undefined, and their infrequent occurrence has further impeded the identification of risk factors. Furthermore, the increasing incidence of small intestinal cancers in the United States and Europe remains incompletely understood, although advances in diagnostic testing, changes in classification schemes, and reporting to cancer registries may contribute to these findings (5-12). Carcinoid tumors, in particular, were not classified as malignant until the second edition of the International Classification of Disease for Oncology in 1990 (13) and only became reportable to the Surveillance, Epidemiology and End Results (SEER) Program in 1992. Appendiceal carcinoid tumors continue to be nonreportable unless expressly designated malignant.

In contrast to multiple studies that have evaluated temporal trends of small intestinal cancers (1, 4-7, 10, 11), fewer studies have described age-specific incidence according to histology (1, 8, 10, 14), and none have considered age-specific rates according to subsite. Although

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multiple series have described racial patterns among blacks and whites (2, 4, 6, 8, 10, 12), age-specific IRs of small intestinal cancers among other racial/ethnic groups, including Hispanics and Asians/Pacific Islanders (API) have rarely been reported (15). Furthermore, population-based studies have described variable improvement in survival among individuals with small intestinal cancers according to histology (5, 7, 9, 11, 16).

In an effort to advance our understanding of small intestinal cancers, we assessed incidence and relative survival (RS) rates in the (SEER) Program. We undertook a complete evaluation of epidemiologic characteristics including age-specific patterns and temporal trends according to histology, gender, racial/ethnic groups, and subsite. We limited our evaluation to a more recent time period—1992 to 2006—to minimize the influence of changing classification schemes and reporting practices over time, and to allow analysis of patterns among Hispanics and APIs.

Materials and Methods

We assessed incidence of small intestinal cancers among residents of 12 cancer registry areas in the SEER Program (SEER-12), which includes the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the areas of Detroit, MI; San Francisco, Los Angeles, and San Jose-Monterey, CA; Seattle-Puget Sound, WA; and Atlanta and rural Georgia (17). These geographic areas include ~14% of the U.S. population. We excluded incident cases that were not microscopically confirmed (n = 179) and those occurring among American Indians/Alaskan Natives (n = 44) or individuals of unspecified or unknown race (n = 42). Use of data from SEER-12 allowed us to maximize the number of cases diagnosed among Hispanics and APIs.

The SEER Program classified topography and histology information according to the International Classification of Diseases for Oncology (ICD-O) second edition for cases diagnosed during 1992 to 2000 and third edition for cases diagnosed during 2001 to 2006 (13, 18); all data have been recoded to ICD-O-3. We considered all cancers of the small intestine (ICD-O topography codes C17.0-C17.9) with malignant behavior (ICD-O behavior code/3) diagnosed during 1992 to 2006 in four broad categories: carcinomas, neuroendocrine cancers, sarcomas, and lymphomas (ICD-O-3 histology codes are detailed in Table 1).

Incidence

IRs, IR ratios (IRR), and 95% confidence intervals (CI) were calculated using the Rate Session in SEER*Stat, version 6.5.1 (17). IRs were age adjusted to the 2000 U.S. standard population and expressed per 100,000 person-years. We assessed IRs overall and according to gender (male, female), racial/ethnic group (non-Hispanic whites, Hispanic whites, blacks, and APIs), stage (localized, regional, distant, and unspecified), and subsite [duodenum (C17.0); jejunum (C17.1); ileum, including Meckel's diverticulum (C17.2-17.3); and unspecified site, including overlapping sites (C17.8-17.9)]. Unless otherwise specified, we refer to non-Hispanic whites as "whites" and Hispanic whites as "Hispanics." To further explore sex-specific patterns of lymphoma, we assessed B-cell lymphomas according to two broad subgroups: intermediate-/high-grade histologies (M-9675, M-9680, M-9684, and M-9687) and low-grade or indolent lymphomas (M-9670, M-9671, M-9673, M-9690, M-9691, M-9695, M-9698, and M-9699).

Staging of small intestinal cancers differs according to histologic subtype, and staging classifications have changed over time. During 1992 to 2006 several staging schemes were used in the SEER Program (19), resulting in the downstaging (distant > regional) or upstaging (localized > regional) of some small intestinal cancers (20). Despite these changes, we used the SEER historic stage variable in our analysis, as similarly done in other SEER-based studies of small intestinal cancers (21), to provide a general overview of staging across small intestinal cancers of different histologies.

Age-specific IRs (<15, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, and 75+ y) and temporal trends (1992-1996, 1997-2001, and 2002-2006) were calculated and depicted on a log-linear scale as previously described (22). As per the SEER Program convention, IRs are not presented for fewer than 16 cases (23).

Survival

Survival analyses included all cases of small intestinal cancer with malignant behavior diagnosed among residents in SEER-12 during 1992 to 2005 and followed through 2006. One- and 5-year RS was estimated using the actuarial method in the SEER*Stat Survival Session. RS is the ratio of the proportion of observed survivors in a cohort of patients to the proportion of expected survivors in a comparable cohort of the general population (19). We estimated RS overall, according to gender, age, stage, and subsite as described above, and two 7-year calendar periods (1992-1998 and 1999-2005). Survival analyses according to stage should be interpreted in the context of changes in staging occurring over time, as noted above. Because life table calculations that provide the expected survival are not available for every racial/ethnic group (19), analysis by race was limited to all whites (Hispanics and non-Hispanics combined) and blacks.

Compared with the general population, individuals with small intestinal cancer have an 11% increased risk of developing a subsequent cancer and a >7-fold risk of developing a new primary small intestinal cancer (24). Given that the survival of individuals with multiple primary cancers may differ from that of those with a single primary small intestinal cancer, we excluded individuals with subsequent primary cancers (n = 2,303). In addition, cases diagnosed by death certificate or autopsy (n = 73) and those alive with unknown survival

Table 1. ICD-O histology codes, IRs, and RS of patients with small intestinal cancers, SEER 12, 1992 to 2006

	ICD-O-3 codes	Incidence*		Survival†		
		No.	Rate	No.	1-y RS (%)	5-y RS (%)
Total		10,945	2.10	7,052	76.3	59.7
Carcinomas						
Adenocarcinomas						
NOS	8140	2,368	0.46	1,438	53.5	28.1
Mucin-producing/mucinous	8480, 8481, 8490	483	0.09	309	59.3	23.8
Arising in adenoma	8210, 8261, 8263	311	0.06	188	67.7	36.7
Other specified	8144, 8145, 8201, 8211, 8255, 8260, 8262, 8310, 8323, 8441, 8452, 8460, 8500	65	0.01	35	61.8	32.5
Other specified	8070, 8082, 8120, 8560	18	<0.01	9	~	~
NOS	8010, 8012, 8020, 8021, 8022, 8032, 8033, 8046, 8510	167	0.03	94	27.8	21.1
Neuroendocrine cancers						
Differentiated (carcinoids)						
Carcinoid, NOS	8240	3,896	0.75	2,489	91.9	82.4
Hormone specific	8153, 8156, 8241	32	0.01	24	~	~
Undifferentiated						
Large cell	8013, 8246	328	0.06	229	87.8	66.7
Small cell	8041	6	~	5	~	~
Atypical carcinoid	8249, 8574	10	~	5	~	~
Mixed endocrine-exocrine	8154, 8243, 8244, 8245	43	0.01	28	92.0	59.3
Sarcomas						
GIST	8935, 8936	616	0.12	396	93.3	70.3
Leiomyosarcoma	8890, 8891, 8895, 8896	307	0.06	206	84.2	44.3
Other specified	8825, 8830, 8851, 8852, 8853, 8858, 8901, 8930, 8940, 8980, 8990, 9044, 9120, 9133, 9140	76	0.01	52	56.6	38.8
Undifferentiated	8800, 8801, 8802, 8803, 8804	85	0.02	50	73.6	43.8
Lymphomas						
B cell						
Large cell	9675, 9680, 9684	1,006	0.19	691	66.1	56.6
Follicular	9690, 9691, 9695, 9698	351	0.07	252	95.6	90.7
MALT	9699	170	0.03	117	86.1	71.9
Diffuse	9670, 9671, 9673	85	0.02	58	82.1	70.7
Burkitt	9687	77	0.01	62	70.3	63.7
Other specified	9650, 9652, 9727, 9728, 9734, 9755, 9758, 9764	16	<0.01	13	~	~
T cell	9702, 9714, 9717, 9719	87	0.02	63	50.6	34.9
NHL and lymphoma NOS	9590, 9591	231	0.04	163	66.6	52.6
Other specified malignancies						
Melanoma	8720, 8730	9	~	5	~	~
Mesothelioma	9050, 9052, 9053	5	~	2	~	~
Germ cell and gonadal stromal tumors	8590, 9064, 9100	3	~	3	~	~
Neuroepithelial and peripheral nerve sheath	8680, 9364, 9473, 9540, 9560	13	~	9	~	~
Myeloid sarcoma	9930	3	~	3	~	~
Unspecified malignancies	8000, 8001, 8004	78	0.02	54	68.8	50.9

Abbreviations: No., number of cases; ~, incidence and RS rates are not presented for fewer than 16 and 25 cases, respectively; GIST, gastrointestinal stromal tumor; NHL, non–Hodgkin lymphoma.

*IRs are age-adjusted to the 2000 U.S. standard population and expressed per 100,000 person-years.

†RS is based on cases diagnosed during 1992 to 2005 and followed through 2006.

Table 2. Age-adjusted IRs and IRRs of small intestinal cancers according to histology, gender, race, stage, and subsite, SEER-12, 1992 to 2006

Characteristic	Carcinomas				Neuroendocrine cancers				Sarcomas				Lymphomas			
	No.	IR	IRR	(95% CI)	No.	IR	IRR	(95% CI)	No.	IR	IRR	(95% CI)	No.	IR	IRR	(95% CI)
Total	3,412	0.66	~		4,315	0.83	~		1,084	0.20	~		2,023	0.38	~	
Gender																
Females	1,618	0.55	1.00	(Reference)	2,013	0.70	1.00	(Reference)	489	0.17	1.00	(Reference)	759	0.26	1.00	(Reference)
Males	1,794	0.80	1.45	(1.35-1.55)	2,302	1.00	1.42	(1.34-1.51)	595	0.24	1.43	(1.27-1.62)	1,264	0.54	2.06	(1.88-2.26)
Race*																
Whites	2,340	0.63	1.00	(Reference)	3,246	0.88	1.00	(Reference)	732	0.20	1.00	(Reference)	1,522	0.42	1.00	(Reference)
Hispanics	254	0.53	0.84	(0.73-0.96)	288	0.56	0.64	(0.56-0.72)	107	0.18	0.92	(0.73-1.14)	189	0.31	0.75	(0.63-0.89)
Blacks	575	1.29	2.06	(1.87-2.26)	648	1.43	1.63	(1.50-1.78)	93	0.19	0.93	(0.74-1.16)	120	0.24	0.58	(0.47-0.70)
APIs	243	0.48	0.77	(0.67-0.88)	133	0.25	0.29	(0.24-0.34)	152	0.27	1.36	(1.13-1.62)	192	0.36	0.87	(0.74-1.01)
Stage																
Localized	780	0.15	1.00	(Reference:)	1,586	0.31	1.00	(Reference)	520	0.10	1.00	(Reference)	N/A	N/A		
Regional	1,292	0.25	1.66	(1.51-1.81)	1,473	0.28	0.93	(0.86-1.00)	224	0.04	0.43	(0.37-0.50)	N/A	N/A		
Distant	1,062	0.21	1.36	(1.24-1.49)	1,051	0.20	0.66	(0.61-0.71)	258	0.05	0.50	(0.43-0.58)	N/A	N/A		
Unspecified	278	0.05	0.36	(0.31-0.42)	205	0.04	0.13	(0.11-0.15)	82	0.02	0.15	(0.12-0.19)	N/A	N/A		
Subsite																
Duodenum	1,888	0.37	1.00	(Reference)	818	0.16	1.00	(Reference)	196	0.04	1.00	(Reference)	394	0.07	1.00	(Reference)
Jejunum	583	0.11	0.30	(0.28-0.33)	231	0.04	0.28	(0.24-0.33)	277	0.05	1.43	(1.18-1.72)	314	0.06	0.81	(0.70-0.94)
Ileum	437	0.08	0.23	(0.21-0.25)	1,966	0.38	2.39	(2.20-2.59)	203	0.04	1.06	(0.87-1.30)	507	0.10	1.29	(1.13-1.47)
Unspecified	504	0.10	0.26	(0.24-0.29)	1,300	0.25	1.59	(1.46-1.74)	408	0.08	2.11	(1.77-2.52)	808	0.15	2.07	(1.83-2.34)
Stage and subsite†																
Duodenum																
Localized	356	0.07	1.00	(Reference)	572	0.11	1.00	(Reference)	77	0.02	1.00	(Reference)	N/A	N/A		
Regional	730	0.14	2.05	(1.80-2.33)	58	0.01	0.10	(0.07-0.13)	46	0.01	0.60	(0.40-0.87)	N/A	N/A		
Distant	565	0.11	1.59	(1.39-1.82)	61	0.01	0.11	(0.08-0.14)	31	0.01	0.40	(0.25-0.61)	N/A	N/A		
Jejunum																
Localized	164	0.03	1.00	(Reference)	76	0.02	1.00	(Reference)	161	0.03	1.00	(Reference)	N/A	N/A		
Regional	229	0.04	1.40	(1.14-1.73)	92	0.02	1.20	(0.87-1.64)	45	0.01	0.28	(0.19-0.39)	N/A	N/A		
Distant	179	0.03	1.09	(0.88-1.35)	60	0.01	0.78	(0.55-1.11)	60	0.01	0.37	(0.27-0.51)	N/A	N/A		
Ileum																
Localized	133	0.03	1.00	(Reference)	529	0.10	1.00	(Reference)	99	0.02	1.00	(Reference)	N/A	N/A		
Regional	174	0.03	1.30	(1.03-1.64)	855	0.16	1.62	(1.45-1.81)	49	0.01	0.49	(0.34-0.70)	N/A	N/A		
Distant	118	0.02	0.88	(0.68-1.14)	544	0.10	1.03	(0.91-1.16)	47	0.01	0.48	(0.33-0.69)	N/A	N/A		

NOTE: IRs are age-adjusted to the 2000 U.S. standard population and expressed per 100,000 person-years. IRRs are based on unrounded rates.

Abbreviations: N/A, data not available.

*Whites include non-Hispanics only; Hispanics include whites only.

†Excludes cases with unspecified stage or unspecified subsite.

time (n = 13) were also excluded from analysis (19). RS rates based on fewer than 25 cases are not presented (23).

Results

In total, 10,945 small intestinal cancers (IR = 2.10/100,000 person-years) were diagnosed among residents of SEER-12 during 1992 to 2006 (Table 1). Neuroendocrine cancers (n = 4,315, IR = 0.83), carcinomas (n = 3,412, IR = 0.66), lymphomas (n = 2,023, IR = 0.38), and sarcomas (n = 1,084, IR = 0.20; Table 2) accounted for ~39%, 31%, 18%, and 10% of small intestinal malignancies, respectively. Sixty-nine percent of carcinomas were adenocarcinoma, not otherwise specified (NOS; n = 2,368; IR = 0.46); 90% of neuroendocrine cancers were carcinoid, NOS (n = 3,896; IR = 0.75); 57% of sarcomas were gastrointestinal stromal tumors (n = 616; IR = 0.12); and 50% of lymphomas were large cell lymphoma, B cell (n = 1,006; IR = 0.19).

For all four major histologic groups, males had significantly higher IRs than females, ranging from 42% to

45% higher for carcinomas, neuroendocrine cancers, and sarcomas, to 106% higher for lymphomas. Compared with whites, Hispanics and APIs had significantly lower IRs of carcinomas (IRR = 0.84 and 0.77, respectively) and neuroendocrine cancers (IRR = 0.64 and 0.29, respectively), whereas blacks had significantly higher IRs for both entities (IRR = 2.06 and 1.63, respectively). The incidence of sarcomas was highest among APIs, and IRs were generally similar among whites, Hispanics, and blacks. Lymphomas were the only cancers that predominated among whites. Carcinomas were associated with significantly higher IRs of regional (IRR = 1.66) and distant disease (IRR = 1.36) compared with localized disease, whereas neuroendocrine cancers and sarcomas had significantly lower IRs for regional (IRR = 0.93 and 0.43, respectively) and distant (IRR = 0.66 and 0.50, respectively) stage compared with localized disease. More than thrice as many carcinomas arose in the duodenum than in the jejunum and ileum. In contrast, more than twice as many neuroendocrine cancers arose in the ileum than the duodenum, and the jejunum was a rare primary site. The subsite was less frequently specified for sarcomas and lymphomas, and the specified cases were more evenly distributed across the subsites. For carcinomas at all subsites, the incidence of regional disease was significantly higher than localized disease; in contrast, sarcomas at all subsites were associated with the highest incidence of localized disease. Neuroendocrine cancers in the duodenum generally presented at localized stage, whereas those in the ileum were predominantly diagnosed with regional disease.

Except for neuroendocrine cancers diagnosed at the youngest ages, all histologic subtypes predominated among males across all age groups (Fig. 1). IRs for carcinomas, neuroendocrine cancers, and sarcomas among both sexes and lymphomas among females tended to

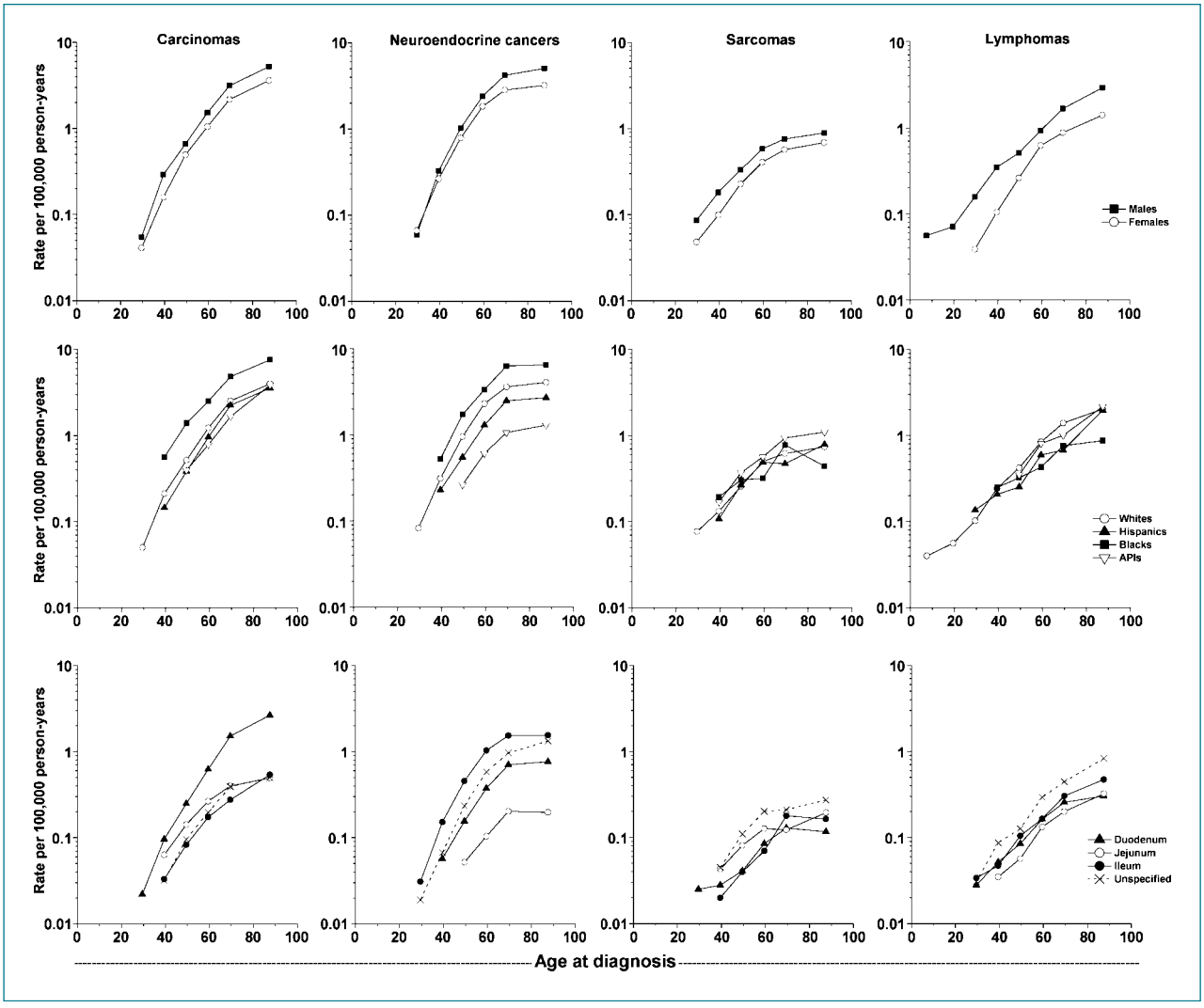

Figure 1. Age-specific IRs of small intestinal cancers according to histology, gender, racial/ethnic group, and subsite, SEER-12, 1992 to 2006.

increase more rapidly across the young adult ages than the older ages. In contrast to the other histologic groups, lymphoma age-specific IR patterns differed by gender. Whereas males had an initial peak in incidence at approximately ages 35 to 44 years and a progressive increase in incidence at older ages, this early peak in IR was not apparent among females. The higher incidence of carcinomas and neuroendocrine cancers among blacks than any other racial/ethnic group was apparent across all age groups. The racial differences in neuroendocrine cancer rates were pronounced across all age groups, whereas carcinoma rates among nonblacks were similar. Age-specific racial/ethnic differences were less pronounced for the sarcomas and lymphomas. Carcinoma of the duodenum IRs increased logarithmically with age, a pattern distinct from that of carcinomas of the jejunum and ileum. In contrast, age-specific rates for neuroendocrine cancers were quantitatively distinct, but patterns were similar across subsites. Sarcomas and lymphomas were characterized by generally similar subsite IRs.

During 1992 to 2006 neuroendocrine cancer IRs increased notably among both males and females, across all racial/ethnic groups, and especially for cancers arising in the duodenum (Fig. 2). Carcinoma rates increased somewhat among males but not females, among blacks and whites but not Hispanics or APIs, and for duodenal carcinomas but not for other subsites. Sarcoma and lymphoma rates did not change greatly during this time period, although duodenal rates increased each type.

When B-cell lymphoma subtypes were considered by gender, the peak in IR at ages 35 to 44 years was limited to males with intermediate-/high-grade histologies (Fig. 3). Age-specific rates for indolent lymphomas were similar at ages <65 years, but rates among males ages 65+ years were about twice those among females. During the study time period, IRs remained generally stable for the more aggressive subtypes, whereas IRs for low-grade lymphomas increased, particularly among women.

Overall RS for all small intestinal cancers was 76.3% at 1 year and 59.7% at 5 years (Table 1). Among the individual histologic entities, follicular B-cell lymphomas were associated with the best RS, exceeding 90% at 1 and 5 years, whereas carcinomas, NOS were associated with the poorest RS (27.8% at 1 year and 21.1% at 5 years). In combination, neuroendocrine cancers were associated with the most favorable 1- and 5-year RS (91.4% and 80.7%, respectively), and carcinomas had the least favorable (54.5% and 28.0%, respectively; Table 3). Survival did not vary substantially by gender or race. For all histologic subtypes, individuals <60 years at diagnosis had consistently better survival than older individuals. Over the two study periods, 5-year survival modestly improved for individuals with carcinomas or neuroendocrine cancers, whereas more notable gains in survival were evident for sarcomas and lymphomas. Survival rates declined most profoundly with advancing stage for carcinomas. Individuals with carcinomas or neuroendocrine cancers involving the duodenum had worse 1- and 5-year RS than those involving the jejunum and ileum. Five-year RS was generally less favorable for sarcomas involving the duodenum and the ileum, and for lymphomas involving the jejunum. Notably, patients with localized stage carcinoma of the duodenum had less favorable 1- and 5-year RS than those with localized carcinoma of the jejunum or ileum.

Discussion

This is among the first population-based studies to comprehensively evaluate small intestinal cancer incidence and survival according to histology, gender, race/ethnicity, stage, and subsite. We found distinct age-specific IRs for carcinomas, neuroendocrine cancers, sarcomas, and lymphomas, thereby supporting the notion that these malignancies differ in their cells of origin and risk factors, as recently reviewed (4). All four histologic subtypes of small intestinal cancers predominated among males, with distinct age-specific patterns among males and females limited to lymphomas. Generally similar age-specific patterns were noted according to racial/ethnic group, although racial differences in susceptibility according to histology were notable for neuroendocrine cancers and, to a lesser extent, for carcinomas. IRs varied by subsite, with carcinomas arising more frequently in the duodenum and neuroendocrine cancers occurring more commonly in the ileum. Temporal patterns varied by gender, racial/ethnic group, and subsite, suggesting that improved medical detection of small intestinal tumors may not fully account for the changes that have been observed in IRs over time.

Carcinomas, neuroendocrine cancers, sarcomas, and, most notably, lymphomas, predominated among males. In general, higher small intestinal cancer IRs have been described among males in North America, Europe, Asia, and Central/South America, with exceptions noted in Iceland, Italy, Poland, Brazil, Australia, and Japan, where IRs are higher among females (2, 8, 14). The male predominance of small intestinal cancers is similar to that described for carcinomas at many other primary sites, a pattern that is attributed, in part, to environmental, endogenous, and behavioral factors that differ by gender (25). In the United States, neuroendocrine cancer IRs at sites other than the small intestine are reported to vary by gender, with those in the colon predominating among males and those in the lung and stomach predominating among females (26). In contrast, in the United Kingdom, higher IRs of gastrointestinal carcinoids and thoracic carcinoids have been found among women before age 50 years but not at older ages (27). Although detection bias related to more laparoscopic procedures among women has been suggested to explain gender differences in abdominal carcinoids (28), this is unlikely to explain the predominance at other sites (27). Hormonal influences have also been implicated in the development of neuroendocrine cancers (27), although gender disparities by site

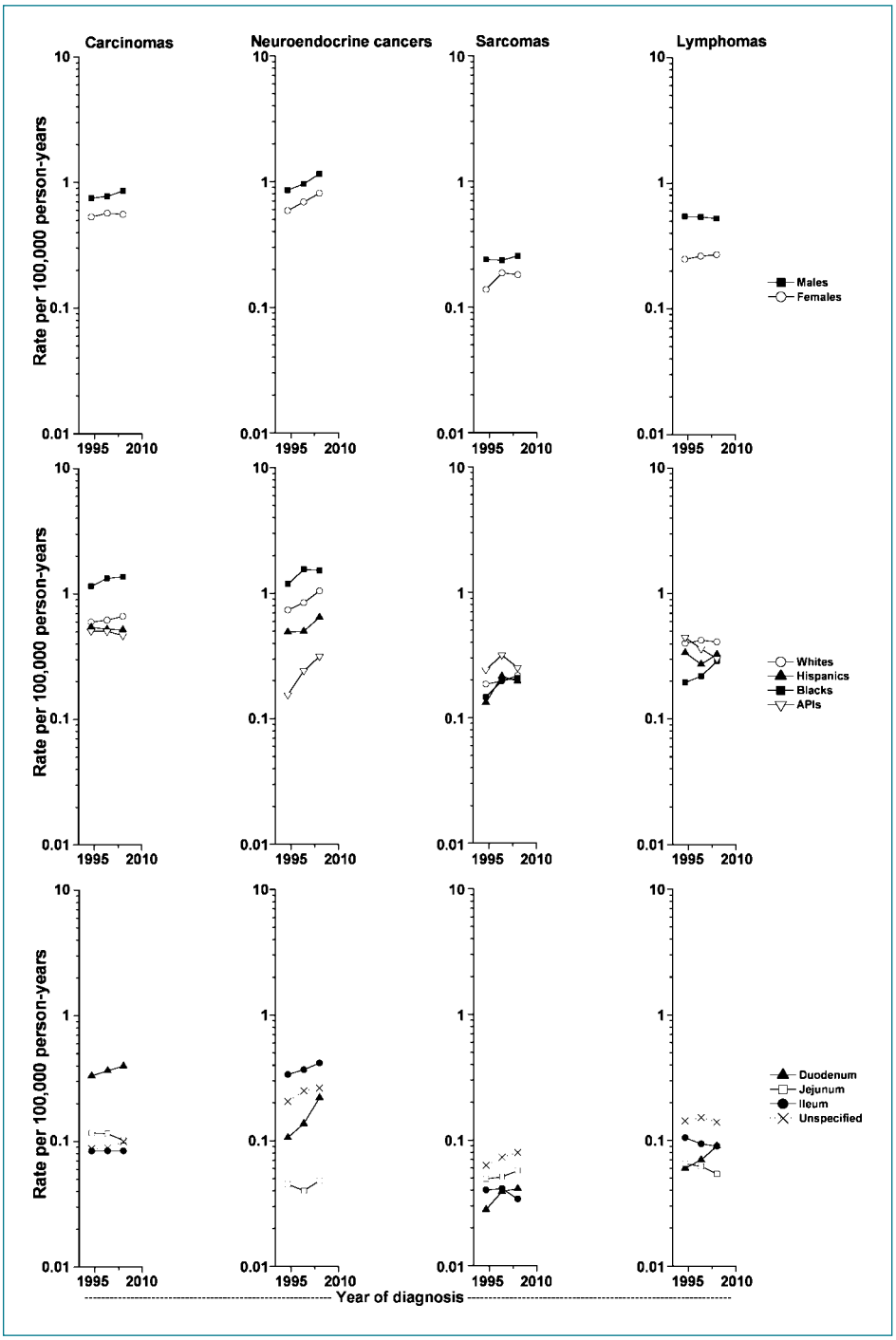

Figure 2. Trends in age-adjusted IRs of small intestinal cancers according to histology, gender, racial/ethnic group, and subsite, SEER-12, 1992 to 2006.

remain poorly understood. Findings that neuroendocrine tumors involving the duodenum/upper jejunum occur more frequently among males, whereas no gender predilection exists for those occurring in the distal jejunum/ileum, suggest that subsite may be another important factor contributing to gender differences (29).

Small intestinal lymphomas are uniquely characterized by a peak in IR in young adulthood among males but not females, and this finding was limited to the more aggressive, intermediate-/high-grade B-cell subtypes. An association of small intestinal lymphoma with HIV infection is suggested by the male predominance, age pattern, HIV-associated histologies, and extranodal subsite, as previously described (30-32). Notably, a similar peak in age-specific IRs is not apparent in studies of small intestinal lymphoma largely encompassing calendar years

before the HIV pandemic (1, 14). With the introduction of highly active antiretroviral therapy in 1996, non–Hodgkin lymphoma IRs have declined in Western countries (30, 31). Although we did not observe a marked change in the trend of intermediate-/high-grade lymphomas, this may reflect the fact that our study largely encompassed the post–highly active antiretroviral therapy time period. The increasing incidence of indolent lymphomas, particularly among women, may be related to specific histologic subtypes included therein. A dramatic increase in IRs of mucosa-associated lymphoid tissue (MALT) lymphoma at all sites combined has been described in the SEER Program (33). Specific organisms have been implicated in MALT lymphomagenesis at specific sites, including *Helicobacter pylori* and gastric MALT (34), and *Chlamydia psittaci* and MALT of the ocular adnexa (35). Although *Campylobacter jejuni* has been suggested to be linked with MALT lymphoma of the small intestine (36), confirmatory studies are needed to establish causality, particularly because *C. jejuni* is not a persistent colonizer of the human intestinal tract (37). Autoimmune disorders, including celiac disease, predispose to small intestinal lymphoma, although the latter is typically associated with lymphomas of T-cell subtype (38). Additional study of indolent lymphomas by subtype is needed to elucidate potential etiologies that may explain the increasing temporal trends, particularly among women.

Most studies that have evaluated the incidence of small intestinal cancers by race have been undertaken using the SEER Program data and describe higher overall small intestinal cancer IRs among blacks compared with whites (4, 6, 8, 10, 12). This is similar to our findings for carcinomas

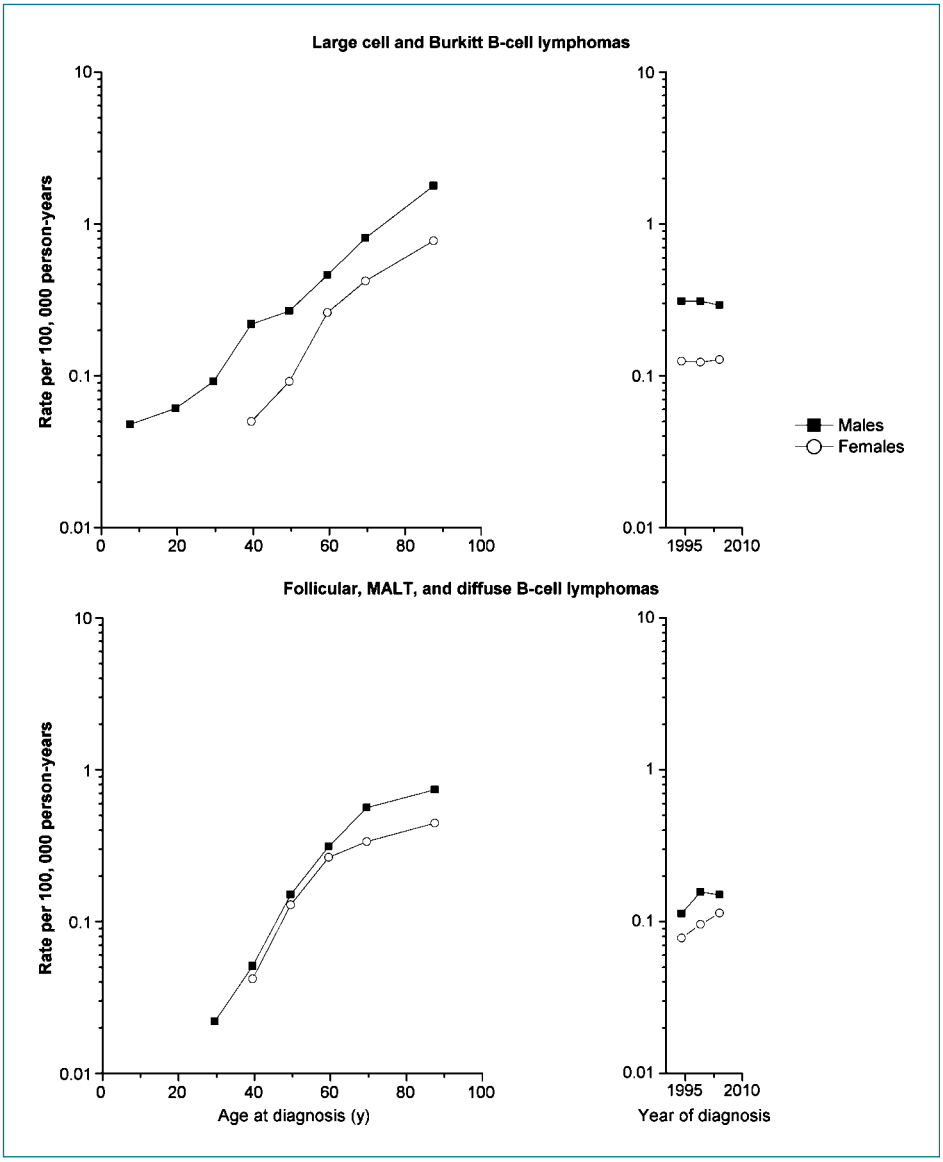

Figure 3. Age-specific IRs and trends in age-adjusted IRs of lymphomas of the small intestine according to histology and gender, SEER-12, 1992 to 2006.

Table 3. RS of small intestinal cancers according to histology, gender, race, age, calendar year, stage, and subsite, SEER-12, 1992 to 2005

Characteristic	Carcinomas			Neuroendocrine cancers			Sarcomas			Lymphomas		
	No.	1 y (%)	5 y (%)	No.	1 y (%)	5 y (%)	No.	1 y (%)	5 y (%)	No.	1 y (%)	5 y (%)
Total	2,073	54.5	28.0	2,780	91.4	80.7	704	86.5	57.9	1,419	73.4	64.1
Gender												
Females	988	54.3	28.1	1,346	91.7	80.9	317	89.0	63.3	518	77.1	72.7
Males	1,085	54.8	27.8	1,434	91.2	80.6	387	84.5	53.4	901	71.3	58.9
Race												
Whites	1,655	54.5	29.0	2,354	92.2	81.8	632	87.8	58.7	1,329	73.4	64.1
Blacks	418	54.6	24.2	426	87.2	75.0	72	75.0	51.1	90	73.8	62.7
Age (y)												
<60	716	66.3	33.8	1,111	96.4	86.5	377	89.8	60.7	653	77.3	66.7
60+	1,357	48.0	24.0	1,669	88.0	76.2	327	82.6	54.4	766	70.0	60.9
Calendar year												
1992-1998	974	54.1	25.9	1,155	89.7	78.1	309	82.5	45.0	676	68.7	56.4
1999-2005	1,099	54.9	30.5	1,625	92.6	83.6	395	89.6	69.5	743	77.7	71.6
Stage												
Localized	423	77.8	57.5	905	91.4	88.5	322	97.0	74.8	N/A	N/A	N/A
Regional	802	69.0	35.4	998	95.7	89.6	151	85.9	53.6	N/A	N/A	N/A
Distant	695	27.6	3.8	757	87.5	63.9	173	74.2	37.0	N/A	N/A	N/A
Unspecified	153	36.5	14.2	120	77.7	59.1	58	64.3	33.3	N/A	N/A	N/A
Subsite												
Duodenum	1,168	47.3	24.5	491	87.8	77.5	132	76.6	55.4	282	75.8	65.9
Jejunum	380	70.8	33.6	161	93.0	80.1	181	93.3	63.6	227	74.1	60.3
Ileum	256	64.9	40.3	1,290	93.9	84.3	115	90.0	56.5	338	76.0	69.4
Unspecified	269	52.8	22.6	838	89.1	76.9	276	85.4	55.3	572	70.4	59.6
Stage and subsite*												
Duodenum												
Localized	204	66.0	46.4	344	92.9	85.6	48	99.5	82.8	N/A	N/A	N/A
Regional	457	66.3	34.3	35	86.9	77.2	27	72.1	47.7	N/A	N/A	N/A
Distant	371	19.0	3.5	32	66.6	40.9	23	~	~	N/A	N/A	N/A
Jejunum												
Localized	98	94.0	68.3	40	95.2	83.3	98	97.3	70.5	N/A	N/A	N/A
Regional	152	79.5	34.7	69	91.5	82.2	35	90.6	58.3	N/A	N/A	N/A
Distant	126	42.2	3.0	51	91.7	72.5	39	89.5	54.9	N/A	N/A	N/A
Ileum												
Localized	68	82.3	71.3	300	92.5	90.9	58	96.4	63.8	N/A	N/A	N/A
Regional	112	69.5	41.3	582	97.6	92.5	28	87.0	62.4	N/A	N/A	N/A
Distant	72	38.7	8.1	387	89.4	68.2	27	76.6	30.8	N/A	N/A	N/A

NOTE: RS is based on cases diagnosed during 1992 to 2005 and followed through 2006.
Abbreviation: ~, survival rates are not presented for fewer than 25 cases.
*Excludes cases with unspecified stage or unspecified subsite.

and neuroendocrine cancers, the two most frequently occurring histologic subtypes. Little data are available for comparison among other racial/ethnic groups, although overall small intestinal cancer IRs in Asia and Central/South America are lower than those reported in North America and Europe (8, 14). Assuming that the incidence of carcinomas and neuroendocrine cancers is higher than that of sarcomas and lymphomas worldwide, our data are not inconsistent with these overall findings—with Hispanics and APIs having lower IRs of carcinomas and neuroendocrine cancers than blacks or whites. Notably, APIs had the highest sarcoma IRs of all racial-ethnic groups studied, whereas lymphomas predominated among whites, thereby further supporting racial/ethnic differences in susceptibility by histologic subtype.

For each major histologic subtype of small intestinal cancer, the greatest increase in incidence was observed for duodenal cancers, consistent with detection bias

arising from the increasing use of upper endoscopic studies (39). Importantly, a concurrent decrease in small intestinal cancers at unspecified sites was not noted, indicating that improvement in coding of tumor subsite is unlikely to account for these changes. Despite the potential for early detection and therefore improved survival, duodenal carcinomas were associated with worse RS than localized carcinomas of the jejunum or ileum, suggesting that duodenal carcinomas may be associated with more aggressive disease behavior and/or decreased responsiveness to therapeutic interventions, including more technically difficult surgical resection.

The survival patterns we report for individuals with small intestinal cancers are generally similar to those recently reported (5), with the most favorable to least favorable survival noted for neuroendocrine cancers, lymphomas, sarcomas, and adenocarcinomas. Bilimoria and colleagues did not describe significant differences in risk of death between 1985 to 2000 for individuals with carcinoids, adenocarcinomas, stromal tumors, or lymphomas of the small intestine (5). During 1992 to 2006, we found little improvement in survival for carcinomas or neuroendocrine cancers, in contrast to sarcomas and lymphomas. The latter may reflect more recent therapeutic advances for some sarcomas (e.g., tyrosine kinase inhibitors; ref. 40) and lymphomas (e.g., monoclonal antibodies; refs. 41, 42) compared with the few effective novel treatments for carcinomas (43), which also tend to present at more advanced stages.

The strengths of our study include the large number of cases of small intestinal cancers diagnosed in a population-based setting. In addition, using the ICD-O classification scheme, we clearly defined the pathologic entities included within each histologic group. Limitations include the lack of a centralized pathology review, although only microscopically confirmed cases were included.

Our study is among the first to report IRs and RS of contemporaneously diagnosed small intestinal cancers and to provide a complete description of age-specific rates according to histology, gender, racial/ethnic groups, and subsite. Our findings provide support for the premise that small intestinal cancers are a heterogeneous group of malignancies. To elucidate the etiology of these cancers, future epidemiologic studies will benefit from considering individual histologic subtypes according to gender, race, and subsite. Finally, additional efforts are needed to increase early detection and to introduce novel treatments, in particular, for small intestinal carcinomas.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Gabos S, Berkel J, Band P, Robson D, Whittaker H. Small bowel cancer in western Canada. Int J Epidemiol 1993;22:198–206.
2. Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev 1998;7:243–51.
3. Neugut AI, Santos J. The association between cancers of the small and large bowel. Cancer Epidemiol Biomarkers Prev 1993;2:551–3.
4. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol 2009;19:58–69.
5. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009;249:63–71.
6. Chow JS, Chen CC, Ahsan H, Neugut AI. A population-based study of the incidence of malignant small bowel tumours: SEER, 1973–1990. Int J Epidemiol 1996;25:722–8.
7. Gustafsson BI, Siddique L, Chan A, et al. Uncommon cancers of the small intestine, appendix and colon: an analysis of SEER 1973-2004, and current diagnosis and therapy. Int J Oncol 2008;33:1121–31.
8. Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control 2005;16:781–7.
9. Lepage C, Bouvier AM, Manfredi S, Dancourt V, Faivre J. Incidence and management of primary malignant small bowel cancers: a well-defined French population study. Am J Gastroenterol 2006;101:2826–32.
10. Severson RK, Schenk M, Gurney JG, Weiss LK, Demers RY. Increasing incidence of adenocarcinomas and carcinoid tumors of the small intestine in adults. Cancer Epidemiol Biomarkers Prev 1996;5:81–4.
11. Shack LG, Wood HE, Kang JY, et al. Small intestinal cancer in England & Wales and Scotland: time trends in incidence, mortality and survival. Aliment Pharmacol Ther 2006;23:1297–306.
12. Thomas RM, Sobin LH. Gastrointestinal cancer. Cancer 1995;75:154–70.
13. Percy C, VanHolten V, Muir C, editors. International Classification of Diseases for Oncology. Geneva (Switzerland): World Health Organization; 1990.
14. Stang A, Stegmaier C, Eisinger B, et al. Descriptive epidemiology of small intestinal malignancies: the German Cancer Registry experience. Br J Cancer 1999;80:1440–4.
15. Ross RK, Hartnett NM, Bernstein L, Henderson BE. Epidemiology of

adenocarcinomas of the small intestine: is bile a small bowel carcinogen? Br J Cancer 1991;63:143–5.
16. Pashayan N, Lepage C, Rachet B, Woods LM, Coleman MP. Survival trends for small intestinal cancer in England and Wales, 1971-1990: national population-based study. Br J Cancer 2006;95:1296–300.
17. Surveillance, Epidemiology and End Results (SEER) Program (http://www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER-12 Regs Public-Use, Nov 2008 Sub (1992-2006), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission.
18. Fritz A, Percy C, Jack A, et al, editors. International Classification of Diseases for Oncology. Geneva (Switzerland): World Health Organization; 2000.
19. Ries LAG, Horner MJD, Young JL, Jr. Introduction. In: Ries LAG, Young JL, Jr., Keel GE, Eisner MP, Lin YD, Horner MJ, editors. Cancer Survival Among Adults: U.S. SEER Program, 1988-2001. Bethesda: National Cancer Institute, NIH Publ. No. 07-6215; 2007, p. 1–6.
20. Young JL, Jr., Roffers SD, Ries LAG, Fritz AG, Hurlbut AA, editors. SEER Summary Staging Manual-2000; Codes and Coding Instructions. Bethesda: National Cancer Institute, NIH Pub. No. 01-4969; 2001.
21. Key C, Meisner ALW. Cancers of the esophagus, stomach, and small intestine. In: Ries LAG, Young JL, Jr., Keel GE, Eisner MP, Lin YD, Horner MJ, editors. Cancer Survival Among Adults: U.S. SEER Program, 1988-2001. Bethesda: National Cancer Institute, NIH Publ. No. 07-6215; 2007, p. 23–32.
22. Devesa SS, Donaldson J, Fears T. Graphical presentation of trends in rates. Am J Epidemiol 1995;141:300–4.
23. In: Horner MJ, Ries LAG, Krapcho M, et al, editors. SEER Cancer Statistics Review, 1975-2006. Bethesda (MD): National Cancer Institute; 2009.
24. Stolzenberg-Solomon RZ, Fraumeni JF, Jr., Wideroff L, Albanes D, Curtis RE. New malignanices following cancer of the digestive tract, excluding colorectal cancer. In: Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF, Jr., editors. New malignancies among cancer survivors: SEER cancer registries, 1973-2000. Bethesda: National Cancer Institute, NIH Publ. No. 05-5302; 2006, p. 59–110.
25. Cook MB, Dawsey SM, Freedman ND, et al. Sex disparities in cancer incidence by period and age. Cancer Epidemiol Biomarkers Prev 2009;18:1174–82.
26. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
27. Newton JN, Swerdlow AJ, dos Santos Silva IM, et al. The epidemiology of carcinoid tumours in England and Scotland. Br J Cancer 1994;70:939–42.
28. Thompson GB, van Heerden JA, Martin JK, Jr., et al. Carcinoid tumors of the gastrointestinal tract: presentation, management, and prognosis. Surgery 1985;98:1054–63.
29. Kloppel G, Anlauf M. Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2005;19:507–17.
30. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. Blood 2001;98:2339–44.
31. Kirk O, Pedersen C, Cozzi-Lepri A, et al. Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy. Blood 2001;98:3406–12.
32. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. J Clin Oncol 2005;23:4430–8.
33. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265–76.
34. Zucca E, Bertoni F, Roggero E, Cavalli F. The gastric marginal zone B-cell lymphoma of MALT type. Blood 2000;96:410–9.
35. Ferreri AJ, Guidoboni M, Ponzoni M, et al. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2004;96:586–94.
36. Lecuit M, Abachin E, Martin A, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. N Engl J Med 2004;350:239–48.
37. Parsonnet J, Isaacson PG. Bacterial infection and MALT lymphoma. N Engl J Med 2004;350:213–5.
38. Di Sabatino A, Corazza GR. Coeliac disease. Lancet 2009;373:1480–93.
39. Rondonotti E, Pennazio M, Toth E, et al. Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. Endoscopy 2008;40:488–95.
40. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–80.
41. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–42.
42. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–91.
43. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol 2009;27:2598–603.