A 5-Decade Analysis of 13,715 Carcinoid Tumors

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BACKGROUND. Carcinoid tumors represent an unusual and complex disease spectrum with protean clinical manifestations. This compilation of several large United States-based databases comprising patients from 1950 to 1999 examines 13,715 carcinoid tumors and provides epidemiologic information regarding the natural history and evolution of the detection and diagnosis of this entity.

METHODS. The authors evaluated 10,878 carcinoid tumors that were identified by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) from 1973 to 1999 in addition to 2837 carcinoid tumors that were registered previously by two earlier NCI programs. To the authors' knowledge, this represents the largest current epidemiology series addressing carcinoid tumors to date.

RESULTS. Specific trends in incidence for carcinoid tumors of certain sites were identified. Among the most recently collected subset of data, sites that demonstrated the greatest incidence of carcinoids were the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%). Within the gastrointestinal tract, most carcinoid tumors occurred in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%). For all sites, age-adjusted incidence rates were highest in black males (4.48 per 100,000 population per year). Associated noncarcinoid tumors were frequent in conjunction with small intestinal (29.0%), gastric (20.5%), colonic (20.0%), and appendiceal (18.2%) carcinoids. The highest percentages of nonlocalized lesions were noted for cecal (81.5–83.2%) and pancreatic (71.9–81.3%) carcinoids, whereas the highest percentage of localized disease was found among rectal (81.7%), gastric (67.5%), and bronchopulmonary (65.4%) carcinoids. The best 5-year survival rates were recorded for patients with rectal (88.3%), bronchopulmonary (73.5%), and appendiceal (71.0%) carcinoids; these tumors exhibited invasive growth or metastatic spread in 3.9%, 27.5%, and 38.8% of patients, respectively.

CONCLUSIONS. Carcinoids appear to have increased in overall incidence over the past 30 years; for some sites, this trend has been evident for nearly half a century. Recent marked increases in gastric and rectal carcinoids and a concomitant decrease in appendiceal carcinoid incidence may be due in part to varying rules of registration among the compiled databases examined in this report or to improvements in diagnostic technology; increased awareness of and about carcinoid tumors also may play a significant role. In 12.9% of all patients with carcinoid, distant metastases already were evident at the time of diagnosis; the overall 5-year survival rate for all carcinoid tumors, regardless of site, was 67.2%. These findings bring into question the widely promulgated relative benignity of carcinoid disease. Certain carcinoid tumors, such as those of the rectum, appear to be over-represented among the black and Asian populations within the United States, suggesting the role of genetics in the development of this intriguing disease. ***Cancer* 2003;97: 934–59.** *© 2003 American Cancer Society.*

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Carcinoid tumors are slow-growing malignancies with distinct biologic and clinical characteristics. Although these tumors have long been a source of clinical and pathologic interest, their fundamental biology still eludes precise delineation. Langhans[1] first described a gut carcinoid tumor in 1867, and it was in 1888 that Lubarsch[2] became the first to record such a lesion in detail. Two years later, Ransom[3] provided the first comprehensive descriptions of the classic symptoms of carcinoid syndrome. Oberndorfer[4] first used the word *karzinoide* in 1907 to distinguish these neoplasms, which he believed were benign, from malignant adenocarcinomata. The recognition of carcinoids as endocrine-related tumors was outlined by Gosset and Masson in 1914.[5]

Because these tumors derive from neuroendocrine cell compartments, their frequency of occurrence correlates with the site-density of neuroendocrine cells. Thus, nearly 60% of carcinoid tumors arise along the largest endocrine organ of man, the intestine. Greater than 25% of carcinoid tumors arise within the bronchopulmonary system, reflecting the high density of Kultschitzky cells in the respiratory epithelium. Other carcinoid tumors occur less frequently and in more obscure sites; the biologic and clinical characteristics of these lesions are not as apparent.

It has become apparent that these supposedly benign tumors may not always behave in such a fashion. Because carcinoid tumors differ substantially from conventional gastrointestinal adenocarcinomas in their pathophysiology and outcome, it is imperative that clinicians consider the biology of these lesions in defining appropriate therapy.

It has become apparent that the term *carcinoid* represents a wide spectrum of neoplasms originating from a variety of neuroendocrine cell types. This archaic descriptor, however, fails to convey adequately the pathologic variety of such neoplasms with their vast array of secretory products. Although notable clinical manifestations of carcinoid tumors often are either vague or absent, in approximately 10% of patients, these tumors secrete bioactive mediators that may engender various characteristics of the carcinoid syndrome.[6] Although precise identification of the specific cell type of each neuroendocrine tumor of the gastrointestinal tract is far from complete, the widespread use of endoscopy, ultrasonography, and other advanced imaging modalities has enhanced significantly the identification of previously undetectable lesions and has allowed a more accurate delineation of metastases.

Unfortunately, investigation of the complex nature of endocrine cell function initially was hampered by a lack of experimental techniques applicable to the cell biology of these lesions. Considerable information has been accrued recently, however, regarding their cells of origin, markers of proliferative activity, bioactive products, and production of diverse growth factors.[7–9]

The epidemiology of these relatively rare lesions, which comprise only 0.49% of all malignancies, is of considerable interest. Although the majority of larger reports regarding carcinoid tumors have dealt with an average of 100–300 patients, a fundamental contribution was presented in 1975 by Godwin in his substantial and detailed evaluation of carcinoid tumor incidence, distribution, and survival.[10] A total of 2837 patients identified by the End Results Group (ERG) and the Third National Cancer Survey (TNCS) programs of the National Cancer Institute (NCI) between 1950 and 1971 were examined. Sites of carcinoid tumors included the lung, ovary, biliary system, and the length of the gastrointestinal tract. Among these patients, the appendix represented the site of most reported carcinoids (ERG, 43.9%; TNCS, 35.5%), followed by the rectum (ERG, 15.4%; TNCS, 12.3%), and the ileum (ERG, 10.8%; TNCS, 13.8%). Godwin noted that age-adjusted incidence rates generally were higher in the black population.

Until 1997, Godwin's analysis remained the gold standard for discussion of carcinoid epidemiology. At that time, however, carcinoid data from the NCI Surveillance Research Program was compiled with Godwin's data and examined by Modlin and Sandor,[11] culminating in the epidemiologic analysis of 8305 patients with carcinoid tumors. That review noted an increased incidence of carcinoid tumors over the preceding 20 years and a concomitant decreasing incidence of appendiceal carcinoids.

The objective of this study was to update information regarding carcinoid tumor epidemiology and to create an expanded database derived from reported patients with carcinoid tumors accumulated by the NCI since 1973. This analysis provides information about changes in incidence and behavior of these lesions; such changes may be secondary to novel methods of diagnosis and treatment for patients with these tumors. Thus, the authors evaluated all available patients within the SEER database from 1973 to 1999 which had registered an additional 10,878 patients with carcinoid tumors of various types since the closure of the ERG and TNCS programs. Wherever possible, data were assimilated in a fashion comparable to that reported by Godwin to facilitate comparison of information and to allow the opportunity to evaluate changes that may have occurred throughout the periods 1950–1971 and 1973–1999.

TABLE 1
Characteristics of the Surveillance, Epidemiology, and End Results (SEER) Database and the 1990 United States Population

Characteristic	SEER (1973–1999) (%)	1990 US population (%)
Below poverty level	12	13
High school graduate or higher (persons age > 25 ys)	78	75
Urban areas	89	75
Farm areas	1	2
Foreign-born	15	8

TABLE 2
Carcinoid-Related International Classification of Diseases for Oncology Second Edition Codes Employed for Database Queries

Code descriptor	SEER (1973–1999)
Carcinoid tumor, NOS	8240
Argentaffin carcinoid, NOS	8241
Enterochromaffin-like cell carcinoid, NOS	8242
Goblet cell carcinoid	8243
Composite carcinoid	8244
Atypical carcinoid tumor	8249
Strumal carcinoid	9091

NOS: not otherwise specified.

MATERIALS AND METHODS

The data in this study were extracted from the SEER database, as compiled by the Surveillance Research Program of the NCI from January 1, 1973 to December 31, 1999.[12] The SEER Program succeeded two earlier NCI programs—the ERG and the TNCS—and covers several geographic areas of the United States and its territories.

The Surveillance Research Program accrues patients from registries in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii as well as the metropolitan areas of Detroit and San Francisco–Oakland. In 1974–1975, the metropolitan area of Atlanta and the 13-county Seattle–Puget Sound areas were added. In 1978, 10 predominantly black rural counties in Georgia were included; in 1980, patients from the American Indian populations residing in Arizona were adjoined. Three additional geographic areas participated in the SEER Program prior to 1990: New Orleans, LA (1974–1977); New Jersey (1979–1989); and Puerto Rico (1973–1989). In 1992, the SEER database was expanded to increase coverage of minority populations, including Hispanics, with the addition of Los Angeles County and four counties in the San Jose–Monterey area south of San Francisco.

Selection criteria for these geographic areas included an ability to operate and maintain a high-quality, population-based cancer reporting system as well as coverage of epidemiologically significant population subgroups. The population covered by SEER is comparable to the general United States population with regard to poverty and education, although the SEER population tends to be somewhat more urban and has a greater proportion of foreign-born persons compared with the general United States population (Table 1). The SEER database, thus, has a catchment of approximately 14% of the United States population; the data set includes records on approximately 2.7 million tumors.

The stated goals of the SEER Program are 1) assembling and reporting, on a periodic basis, estimates of cancer incidence and mortality in the United States; 2) monitoring annual cancer incidence trends to identify unusual changes in specific forms of cancer occurring in population subgroups defined by geographic and demographic characteristics; 3) providing continuing information on changes over time in the extent of disease at diagnosis, during therapy, and associated changes in patient survival; and 4) promoting studies designed to identify factors amenable to cancer control interventions.[12] The *International Classification of Diseases for Oncology* (ICD-O) histology codes describing subsets of carcinoid tumor types were included in queries of the SEER database (Table 2).[13] Because the ICD-O definitions have evolved with time, the definition of carcinoid tumors has varied slightly in each subsequent version of this coding schema. This may have influenced the data presented in the current study during comparisons with the ERG and TNCS databases.[14] Because the SEER Program only registered malignant tumors prior to 1986, carcinoid tumors were reported only to the SEER registry during this period if they were designated malignant. However, in classic histologic terminology, carcinoid tumors (except those of the appendix) generally have been considered malignant, and, as such, all are reportable to SEER unless they specifically are designated benign.[4,15,16] In this report, the authors compared the data, as supplied by the SEER Program, with the ERG (1950–1969) and the TNCS (1969–1971) data reported by Godwin in 1975.[10] The ERG was a hospital-based program that was set up to report survival, whereas the TNCS was a population-based incidence-reporting system that was used over a 3-year period. Because distribution by gender, race, and age for the ERG data were remarkably similar to that of the TNCS file, Godwin employed the TNCS database to evaluate age-adjusted incidence rates and to compare carcinoid tumors with other noncarcinoid tumors.[10] Conversely, the ERG data were used as a baseline to analyze carcinoid tumors by stage and to estimate the

TABLE 3
Population Ratios from Decennial Census Data

		Ratio			
Census yr	Applicable SEER subset	Female:male	White:black	Non-Asian:Asian[a]	Non-Hispanic:Hispanic
1980	Early SEER (1973–1991)	1.06	7.11	66.3	14.0
1990	Pan-SEER (1973–1999)	1.05	6.84	32.3	10.1
2000	Late SEER (1992–1999)	1.04	6.10	24.6	6.7

[a] The 1980 and 1990 United States Census grouping for "Asian" included respondents for Japanese, Chinese, Filipino, Korean, Asian Indian, and Vietnamese. However, for the United States Census 2000, respondents were asked to report any *one or more* races they considered themselves; the Year 2000 ratio data corresponds to those indicating "Asian alone."

5-year relative survivals. For this article, specific queries of the SEER database were generated to facilitate comparison of the SEER data with anatomic sites of pathology as reported by Godwin.

In the current study, the entire SEER database was analyzed to generate information regarding the type and distribution of carcinoid tumors. Subanalysis was undertaken, when appropriate, for patients accrued from 1992 through 1999 to investigate trends in incidence (including data from the ERG and TNCS reports) during the periods 1950–1969, 1969–1971, 1973–1991, and 1992–1999. Anatomic sites with patient tallies of less than five were included in all calculations but, to facilitate space management, have not been presented in the accompanying tables. Age-adjusted analyses were completed using the 1970 and 2000 United States standard populations for examination of cases accrued from 1973–1991 and from 1992–1999, respectively. Population-based correction ratios for gender and race were obtained from United States decennial census data for 1980, 1990, and 2000 and were applied to the 1973–1991, 1973–1999, and 1992–1999 SEER data sets, respectively (Table 3).[17] Unfortunately, as in all multisource and time-extended analyses, this study retains certain limitations, including 1) distinct operational rules between the ERG, TNCS, and SEER data (e.g., in the ERG data, all carcinoids were reported, whereas in the TNCS and SEER data, only tumors that were considered malignant were reported prior to 1986), and 2) because only summarized information on the ERG and TNCS data, as reported by Godwin, is available, it was not feasible to undertake the ideal statistical analyses necessary to precisely evaluate the populations and incidences as noted during these earlier periods.

For this analysis, tumor staging was categorized as *localized* if the lesion was described as in situ or was confined to the organ of origin; *regional* if local invasion or lymph node metastasis was present; *distant* if metastatic dissemination to other organs was evident; and *unstaged* if information was insufficient to assign a stage. Statistical evaluation of survival data was undertaken by analysis of variance; data are expressed as the mean ± standard error of the mean, where appropriate.

RESULTS

Site

The distribution of 13,715 carcinoid tumors by site in each of the ERG, TNCS, and SEER Program series as well as the combined set of the three series is shown in Table 4. The following trends are apparent over the 50-year period: Gastric carcinoid tumors, as a percentage of total carcinoid tumors, increased from 2.25% in the ERG series to 5.85% in the most recent SEER subset (1992–1999), whereas small intestinal carcinoid tumors increased from 18.9% to 28.2%. The percentage of cecal carcinoid tumors rose from 2.7% to 4.6% in the 1973–1991 SEER subset but subsequently fell to 3.5% in the 1992–1999, SEER subset. The percentage of rectosigmoid lesions, however, increased between the earliest and most recent data groupings, from 0.80% to 1.94%. Appendiceal carcinoid tumors decreased from 43.9% to 2.4%, although the pan-SEER (1973–1999) database incidence remained 4.77%. The combined group of all gastrointestinal carcinoid tumors has decreased in relative frequency over time (ERG and TNCS, 76.8%; pan-SEER, 64.3%) despite the increasing number of reported gastrointestinal carcinoid tumors (ERG and TNCS, 2301 tumors; pan-SEER, 6996 tumors). This alteration reflects the increase in the percentage of tracheobronchopulmonary carcinoid tumors (ERG, 10.2%; pan-SEER, 27.9%) identified over the past half-century.

Overall, in the combined series of 13,715 carcinoid tumors, 66.9% of all carcinoid tumors occurred in the gastrointestinal tract, whereas the tracheobronchopulmonary complex (24.5%) comprises the most frequent extradigestive site for carcinoid formation. For the most recent SEER subset, most carcinoid tumors within the gastrointestinal tract occurred in the small bowel (41.8% of gastrointestinal carcinoids), with the

TABLE 4
Distribution of 13,715 Carcinoid Tumors by Site: End Results Group, Third National Cancer Survey, and SEER Registries

	ERG (1950–1969)		TNCS (1969–1971)		Early SEER (1973–1991)		Late SEER (1992–1999)		Pan-SEER (1973–1999)		Total carcinoids (1950–1999)
Carcinoid site	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients
All carcinoid sites	1867	—	970	—	5889	—	4989	—	10878	—	13,715
Digestive system	1635	87.57	545	56.19	3626	61.57	3370	67.55	6996	64.31	9176
Esophagus	—	—	—	—	3	0.05	3	0.06	6	0.06	6
Stomach	42	2.25	19	1.96	209	3.55	292	5.85	501	4.61	562
Small intestine	353	18.91	—	—	1697	28.82	1408	28.22	3105	28.54	3458
Duodenum	33	1.77	22	2.27	114	1.94	191	3.83	305	2.80	360
Jejunum	19	1.02	19	1.96	124	2.11	74	1.48	197	1.81	235
Ileum	202	10.82	134	13.81	956	16.23	666	13.35	1623	14.92	1959
Meckel diverticulum	—	—	—	—	25	0.42	27	0.54	52	0.48	52
Overlapping (ileocecum)	14	0.75	—	—	15	0.25	14	0.28	29	0.27	43
Small intestine, NOS	99	5.30	70	7.22	463	7.86	436	8.74	899	8.26	1068
Colon and rectum	1238	66.31	526	54.23	1592	27.03	1523	30.53	3115	28.64	4879
Colon, except appendix	72	3.86	65	6.70	558	9.48	380	7.62	938	8.62	1075
Cecum	50	2.68	29	2.99	271	4.60	173	3.47	444	4.08	523
Appendix	820	43.92	340	35.05	398	6.76	121	2.43	519	4.77	1679
Ascending colon	22	1.18	10	1.03	55	0.93	29	0.58	84	0.77	116
Hepatic flexure	—	—	—	—	13	0.22	7	0.14	20	0.18	20
Transverse colon	14	0.75	3	0.31	27	0.46	10	0.20	37	0.34	54
Spienic flexure	—	—	—	—	9	0.15	6	0.12	15	0.14	15
Descending colon	4	0.21	1	0.10	23	0.39	13	0.26	36	0.33	41
Sigmoid colon	23	1.23	13	1.34	101	1.72	106	2.12	207	1.90	243
Large intestine (colon), NOS	9	0.48	9	0.93	59	1.00	36	0.72	95	0.87	113
Rectosigmoid junction	15	0.80	2	0.21	80	1.36	97	1.94	177	1.63	194
Rectum	281	15.05	119	12.27	556	9.44	925	18.54	1481	13.61	1881
Anus, anal canal, and anorectum	—	—	—	—	9	0.15	9	0.18	18	0.17	18
Liver	—	—	—	—	14	0.24	31	0.62	45	0.41	45
Gallbladder	1	0.05	—	—	7	0.12	17	0.34	24	0.22	25
Other biliary	1	0.05	—	—	11	0.19	18	0.36	30	0.28	31
Pancreas	—	—	—	—	47	0.80	32	0.64	79	0.73	79
Digestive tract, NOS	27	1.45	8	0.82	171	2.90	174	3.49	346	3.18	381
Ovary	—	—	3	0.31	42	0.71	68	1.36	110	1.01	113
Testis	—	—	—	—	3	0.05	5	0.10	8	0.07	8
Other endocrine, including thymus	—	—	—	—	25	0.42	16	0.32	41	0.38	41
Trachea, bronchi, lung	191	10.23	137	14.12	1777	30.17	1260	25.26	3037	27.92	3365

ERG: End Results Group; TNCS: Third National Cancer Survey; NOS: not otherwise specified.

highest frequency in the ileum (47.3% of small bowel carcinoids) (Table 5). For the same period, appendiceal carcinoids comprised 3.47% of all carcinoid tumors and 24.1% of all gastrointestinal carcinoid tumors. In the large bowel, carcinoids clearly occurred most frequently in the rectum (27.4%), followed by the cecum (5.1%). However, it is possible that lesions at the base of the appendix cannot always be distinguished easily from strictly cecal carcinoids; therefore, there may be some inadvertent crossover in the assessment of these two groups. Figure 1 demonstrates the trends in increasing percentages for extraappendiceal carcinoids over the past 50 years as well as the marked decrease in appendiceal carcinoid proportion.

The evaluation of carcinoid tumors by site, race, and gender in the pan-SEER registry (Table 6) revealed a female predominance for gastric, colonic, appendiceal, bronchopulmonary, and gallbladder carcinoids (64.5%, 56.5%, 65.7%, 63.0%, and 75.0%, respectively). There was a slight overall female predominance in all types of carcinoid tumors (55.1%). The strongest evidence of male predominance was noted for esopha-

TABLE 5
Distribution of 9421 Gastrointestinal Carcinoid Tumors by Site: End Results Group, Third National Cancer Survey, and SEER Registries

	ERG (1950–1969)		TNCS (1969–1971)		Early SEER (1973–1991)		Late SEER (1992–1999)		Pan-SEER (1973–1999)		Total carcinoids (1950–1999)
Carcinoid site	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients
Digestive system	1635	—	790	—	3626	—	3370	—	6996	—	9421
Esophagus	—	—	—	—	3	0.08	3	0.09	6	0.09	6
Stomach	42	2.57	19	2.41	209	5.76	292	8.66	501	7.16	562
Small intestine	353	21.59	245	31.01	1697	46.80	1408	41.78	3105	44.38	3703
Duodenum	33	2.02	22	2.78	114	3.14	191	5.67	305	4.36	360
Jejunum	19	1.16	19	2.41	124	3.42	74	2.20	197	2.82	235
Ileum	202	12.35	134	16.96	956	26.37	666	19.76	1623	23.20	1959
Meckel diverticulum	—	—	—	—	25	0.69	27	0.80	52	0.74	52
Overlapping (lleocecum)	14	0.86	—	—	15	0.41	14	0.42	29	0.41	43
Small intestine, NOS	99	6.06	70	8.86	463	12.77	436	12.94	899	12.85	1068
Colon and rectum	1238	75.72	526	66.58	1592	43.91	1523	45.19	3115	44.53	4879
Colon, except appendix	72	4.40	65	8.23	558	15.39	380	11.28	938	13.41	1075
Colon, except rectum	942	57.61	405	51.27	956	26.37	501	14.87	1457	20.83	2804
Cecum	50	3.06	29	3.67	271	7.47	173	5.13	444	6.35	523
Appendix	820	50.15	340	43.04	398	10.98	121	3.59	519	7.42	1679
Ascending colon	22	1.35	10	1.27	55	1.52	29	0.86	84	1.20	116
Hepatic flexure	—	—	—	—	13	0.36	7	0.21	20	0.29	20
Transverse colon	14	0.86	3	0.38	27	0.74	10	0.30	37	0.53	54
Splenic flexure	—	—	—	—	9	0.25	6	0.18	15	0.21	15
Descending colon	4	0.24	1	0.13	23	0.63	13	0.39	36	0.51	41
Sigmoid colon	23	1.41	13	1.65	101	2.79	106	3.15	207	2.96	243
Large intestine (colon), NOS	9	0.55	9	1.14	59	1.63	36	1.07	95	1.36	113
Rectum and rectosigmoid junction	296	18.10	121	15.32	636	17.54	1022	30.33	1658	23.70	2075
Rectosigmoid junction	15	0.92	2	0.25	80	2.21	97	2.88	177	2.53	194
Rectum	281	17.19	119	15.06	556	15.33	925	27.45	1481	21.17	1881
Liver	—	—	—	—	14	0.39	31	0.92	45	0.64	45
Intrahepatic bile ducts	—	—	—	—	0	0.00	1	0.03	1	0.01	1
Gallbladder	1	0.06	—	—	7	0.19	17	0.50	24	0.34	25
Other billary	1	0.06	—	—	11	0.30	18	0.53	30	0.43	31
Pancreas	—	—	—	—	47	1.30	32	0.95	79	1.13	79
Digestive tract, NOS	27	1.65	8	1.01	171	4.72	174	5.16	346	4.95	381

ERG: End Results Group; TNCS: Third National Cancer Survey; NOS: not otherwise specified.

geal carcinoids (66%) and thymic carcinoids (76%). Because each of these latter two groups represented a small number of patients (6 patients and 41 patients, respectively), the strength of this observation is questionable.

Examining the patient tallies by race, the crude number of carcinoid tumors arising in white patients exceeds that for black patients at all sites. However, when the number of tumors in black patients is scaled by the ratio of white to black citizens, as identified in the 1990 United States Census (Table 3), an estimate of the relative race-based incidence can be made. For example, 1990 census data suggest that there are 6.84 white citizens for each black citizen in the United States. For the 882 rectal carcinoids identified in white patients within the pan-SEER database, it is possible to expect that $882 \div 6.84 \approx 129$ rectal carcinoids among black patients, if race played no factor in carcinoid development. However, 318 such tumors were registered. This reveals an actual-to-expected ratio of $318 \div 129 \approx 2.47$ for rectal carcinoids among black patients, suggesting that carcinoid tumors at this site were over-represented among black patients. Similarly, duodenal carcinoids demonstrate an incidence propensity in black patients 3.12 times what would be expected; earlier reports have not demonstrated an equivalently increased occurrence of peptic ulcers in the black population.[18] Bronchopulmonary carcinoids, however, are present in only half of the expected number of black patients. The noncarcinoid lung carcinoma rate for the black population exceeds that of the white population (79.8 vs. 60.6 per 100,000 population, respectively), and the actual number of such noncarcinoid lung carcinomas (34,921 patients)

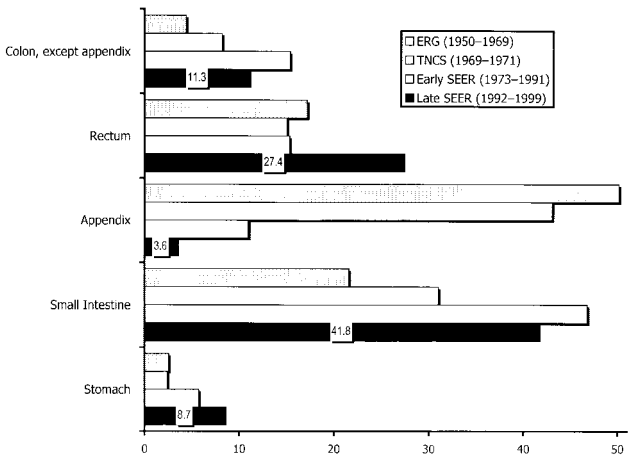

FIGURE 1. Sites of gastrointestinal carcinoid tumors as the percentage of all carcinoid tumors, 1950–1999. ERG: End Results Group; TNCS: Third National Cancer Survey.

closely matches the expected number of patients based on decennial population census ratios (34,490 patients). This supports the finding that although noncarcinoid lung carcinoma occurs in the white population at a frequency greater than or equal to the frequency that is expected in the black population, carcinoids of the lung are less prevalent among the black population than may be expected.

It is interesting to note that the overall population-corrected number of carcinoid tumors in black patients (1311) is essentially equal to the actual number of accrued patients (1309) (Table 6). This further supports the finding that particular sites for carcinoid tumors, rather than carcinoid tumors as a whole, may harbor differential incidence proclivities within this population.

Comparison of Carcinoids with Other Site-Specific Malignancies

The carcinoid and noncarcinoid tumors in the SEER file were compared by site with regard to incidence, average age at diagnosis, male:female ratios, and various race and origin ratios. By using the data from the TNCS series, trends in such ratios over the past 30 years were examined. In the late SEER (1992–1999) subgroup, small intestinal carcinoids maintained a relatively high percentage (43.5%) of all tumors reported at this site. There was a marked increase in the percentage of gastric carcinoids (TNCS, 0.3%; late SEER, 1.77%), whereas the predominance of appendiceal carcinoids decreased notably (TNCS, 77.3%; late SEER, 15.2%). Examining the relative changes in carcinoid presentation by site from the TNCS data set to the late SEER subgroup revealed a 491% increase in gastric carcinoids and a 240% increase for rectal carcinoids between these periods (data not presented). The observed 80% decrement in predominance for appendiceal carcinoids is noteworthy. Comparisons between the early SEER (1973–1991) and late SEER subpopulations revealed similar trends, with increases in predominance of 500%, 194%, 190%, and 137% for gallbladder, ovarian, hepatic, and sigmoid colon carcinoids, respectively. Similar data highlighting the changes from early to late SEER subsets are presented in Figure 2, which also shows the decreases in site-specific predominance for appendiceal and breast carcinoids.

Age, Gender, and Race

In 1975, Godwin opined that patients with carcinoid tumors were generally younger than patients with other tumors; this still appears to be the case. The average age at diagnosis for all carcinoid patients rose from 59.9 years to 61.4 years between the early SEER and late SEER subsets; these values remain slightly lower compared with the values for patients with any noncarcinoid tumor (62.6 years and 63.9 years, respectively, for the early SEER and late SEER subsets; data not presented). Although exceptions to this generalization are identifiable in some areas (such as the liver, larynx, testis, thymus, and retroperitoneum), the low number of tumors reported for these locations obviates any definitive conclusions. The average age at diagnosis for patients with small intestinal carcinoids (65.4 years) is within 2 months of the average age at diagnosis for patients with noncarcinoid tumors at the same site (65.3 years). Although the TNCS series (1969–1971) reported an average age at diagnosis of 35.7 years for patients with appendiceal carcinoids, this value has now risen to 49.3 years within the late SEER subset; the value for noncarcinoid appendiceal tumors has been steady at around 60 years throughout the TNCS, early SEER, and late SEER series. Comparing the limited categories of data from the TNCS series with data from the composite SEER registry suggests an overall increase in the average age at diagnosis for patients with gastrointestinal and bronchopulmonary carcinoids. However, this trend is not consistent across all sites between the early SEER and late SEER subsets.

The crude black:white ratios among patients with carcinoid tumors have remained relatively steady for all types of carcinoids over the evaluated periods (Table 7). The historic 0.36 black:white ratio for gastric carcinoids in the TNCS data set may be anomalous due to the relatively low number of reported carcinoid tumors (Table 4), as the black:white ratio for noncarcinoid gastric tumors has not varied significantly over

TABLE 6
Distribution of 10,878 Carcinoid Tumors by Site, Race, and Gender: SEER Registry, 1973–1999

	No. of patients				No. of patients		All races		
Carcinoid site	White	Black	Other and unknown	Black actual-to-expected ratio[a]	Male	Female	Male %	Female %	Total no. of patients
All carcinoid sites	8965	1309	604	1.00	4880	5998	44.9	55.1	10,878
Digestive system	5484	1019	493	1.27	3388	3608	48.4	51.6	6996
Esophagus	6	0	0	0.00	4	2	66.7	33.3	6
Stomach	407	63	31	1.06	178	323	35.5	64.5	501
Small intestine	2628	401	76	1.04	1628	1477	52.4	47.6	3105
Duodenum	191	87	27	3.12	165	140	54.1	45.9	305
Jejunum	173	19	6	0.75	114	84	57.9	42.6	197
Ileum	1438	155	29	0.74	816	806	50.3	49.7	1623
Meckel diverticulum	48	3	1	0.43	33	19	63.5	36.5	52
Overlapping (ileocecum)	22	5	2	1.55	17	12	58.6	41.4	29
Small intestine, NOS	756	132	11	1.19	483	416	53.7	46.3	899
Colon and rectum	2226	521	368	1.60	1437	1678	46.1	53.9	3115
Colon, except appendix	781	112	45	0.98	408	530	43.5	56.5	938
Cecum	393	46	5	0.80	159	285	35.8	64.2	444
Appendix	454	45	20	0.68	178	341	34.3	65.7	519
Sigmoid colon	145	40	22	1.89	109	98	52.7	47.3	207
Rectum	882	318	281	2.47	766	715	51.7	48.3	1481
Gallbladder	19	2	3	0.72	6	18	25.0	75.0	24
Pancreas	62	12	5	1.32	44	35	55.7	44.3	79
Digestive tract, NOS	239	69	37	1.97	180	166	52.0	48.0	346
Urinary system	7	0	0	0.00	5	2	71.4	28.6	7
Ovary	90	16	4	1.22	0	110	—	100.0	110
Testis	7	0	1	0.00	8	0	100.0	—	8
Other endocrine, induding thymus	38	1	2	0.18	31	10	75.6	24.4	41
Trachea, bronchi, lung	2756	201	80	0.50	1124	1913	37.0	63.0	3037

NOS: not otherwise specified.

[a] The expected number of diagnoses among black patients (not tabularized here) was calculated by scaling the number of observed cases among white patients by the appropriate white:black population ratio, as shown in Table 3. This value was then compared with the actual number of diagnoses among black patients to generate the actual-to-expected ratio.

the time span of this analysis. The crude black:white ratio within the late SEER subset for rectal carcinoids was 0.38, whereas bronchopulmonary carcinoids demonstrated a much lower value (0.07). Population-corrected race ratios (scaling the actual number of reported tumors to an expected number of tumors based on the overall race proportions in the corresponding decennial census as outlined above, using data from Table 3), however, provide additional insight into a possible race-related propensity toward carcinoid development at specific sites. The number of rectal carcinoids in black patients is 2.30 times what would be expected if the black and white populations were in equal proportion and if the incidence for disease between these two races was the same. This finding is even more striking when it is compared with the population-corrected black:white ratio for noncarcinoid tumors of the rectum (0.46), which suggests that noncarcinoid tumors of the rectum occur in black patients at a rate that is less than half of what may be predicted, indicating an out-of-proportion propensity

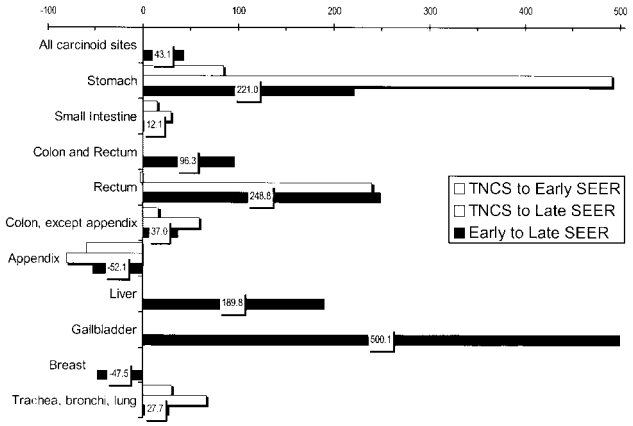

FIGURE 2. Percent change in carcinoids as a proportion of all tumors at a given site, 1969–1999. TNCS: Third National Cancer Survey.

TABLE 7
Black:White Ratios for Carcinoid and Noncarcinoid Tumors by Site: Third National Cancer Survey (1969–1971) and SEER (1973–1991) Registries

	Carcinoid tumors					Noncarcinoid tumor				
	Crude ratios			Corrected[a]		Crude ratios			Corrected[a]	
Carcinoid site	1969–1971	1973–1991	1992–1999	1973–1991	1992–1999	1969–1971	1973–1991	1992–1999	1973–1991	1992–1999
All carcinoid sites	—	0.13	0.17	0.91	1.03	—	0.09	0.11	0.67	0.64
Digestive system	—	0.16	0.22	1.13	1.32	—	0.10	0.12	0.71	0.73
Stomach	0.36	0.16	0.15	1.16	0.91	0.13	0.14	0.18	1.00	1.07
Small intestine	0.17	0.13	0.18	0.94	1.09	0.10	0.13	0.18	0.91	1.07
Colon and rectum	—	0.19	0.28	1.38	1.73	—	0.08	0.10	0.57	0.62
Colon, except appendix	0.13	0.13	0.16	0.94	0.98	0.08	0.09	0.11	0.61	0.67
Colon, except rectum	—	0.12	0.14	0.86	0.85	—	0.09	0.11	0.61	0.67
Cecum	—	0.11	0.13	0.80	0.76	—	0.09	0.11	0.62	0.68
Appendix	0.10	0.10	0.08	0.74	0.51	0.12	0.10	0.10	0.71	0.62
Ascending colon	—	0.06	0.16	0.41	0.98	—	0.08	0.11	0.60	0.68
Hepatic flexure	—	0.08	—	0.59	—	—	0.10	0.10	0.68	0.62
Transverse colon	—	0.04	—	0.27	—	—	0.09	0.10	0.64	0.63
Splenic flexure	—	0.13	—	0.89	—	—	0.14	0.15	1.00	0.88
Descending colon	—	0.31	0.43	2.22	2.61	—	0.12	0.15	0.86	0.94
Sigmoid colon	—	0.25	0.30	1.80	1.83	—	0.07	0.09	0.50	0.57
Large intestine (colon), NOS	—	0.13	0.07	0.95	0.42	—	0.09	0.13	0.63	0.79
Rectum and rectosigmoid junction	—	0.34	0.38	2.44	2.34	—	0.06	0.08	0.45	0.48
Rectosigmoid junction	—	0.40	0.45	2.82	2.72	—	0.06	0.09	0.42	0.54
Rectum	0.36	0.34	0.38	2.38	2.30	0.07	0.07	0.07	0.47	0.46
Anus, anal canal, and anorectum	—	0.29	0.50	2.03	3.05	—	0.11	0.13	0.76	0.80
Liver and intrahepatic bile ducts	—	—	0.15	—	0.90	—	0.16	0.16	1.12	0.95
Liver	—	—	0.15	—	0.94	—	0.17	0.18	1.18	1.11
Gallbladder	—	—	0.13	—	0.81	—	0.06	0.10	0.43	0.62
Other biliary	—	0.33	0.06	2.37	0.36	—	0.08	0.08	0.41	0.47
Pancreas	—	0.18	0.21	1.31	1.27	—	0.12	0.14	0.86	0.86
Digestive tract, NOS	—	0.30	0.33	2.16	2.01	—	0.07	0.09	0.47	0.56
Peritoneum, omentum, and mesentery	—	—	0.18	-	1.11	—	0.05	0.06	0.39	0.35
Breast	—	0.08	0.25	0.55	1.53	—	0.08	0.10	0.56	0.59
Female genital system	—	0.13	0.20	0.89	1.22	—	0.11	0.10	0.80	0.62
Ovary	—	0.14	0.21	0.96	1.27	—	0.06	0.07	0.45	0.45
Endocrine system	—	—	0.08	—	0.47	—	0.07	0.07	0.48	0.46
Other endocrine, including thymus	—	—	0.08	—	0.47	—	0.13	0.15	0.91	0.92
Skin and soft tissue	—	1.00	—	7.11	—	—	0.03	0.03	0.22	0.18
Trachea, bronchi, lung	—	0.07	0.07	0.52	0.45	—	0.11	0.12	0.81	0.74

NOS: not otherwise specified.

[a] Population-corrected data were scaled by ratios as listed in Table 3.

for the development of rectal carcinoid tumors among black patients.

Changes in these ratios over time can be identified by examining data drawn from the early SEER and late SEER subsets. Although the overall black:white carcinoid ratio has increased from 0.93 to 1.03 since 1973, the ratio for the gastrointestinal system as a whole has increased from 1.13 to 1.32, whereas the ratio for the tracheobronchopulmonary complex has fallen from 0.52 to 0.45. Among noncarcinoid tumors, there have been analogous changes at these sites, although to a lesser degree. Across all sites, the population-corrected black:white noncarcinoid tumor incidence rate has fallen from 0.67 to 0.64.

Similar population-corrected ratio analyses were performed comparing Asian with non-Asian patients and Hispanic with non-Hispanic patients. These analyses revealed, in general, high Asian:non-Asian carcinoid ratios and low Hispanic:non-Hispanic ratios for most carcinoid-prone sites. Specifically, Asian patients demonstrated a markedly elevated propensity to the development of colorectal carcinoid tumors, with a population-corrected Asian:non-Asian ratio of 3.41 within the late SEER subset (Table 8). Values within

TABLE 8
Asian:Non-Asian Ratios for Carcinoid and Noncarcinoid Tumors by Site in the SEER (1973–1999) Registry

	Carcinoid tumors				Noncarcinoid tumors			
	Crude ratios		Corrected[a]		Crude ratios		Corrected[a]	
Carcinoid site	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999
All carcinoid sites	0.03	0.06	2.30	1.45	0.04	0.06	2.68	1.48
Digestive system	0.04	0.07	2.95	1.84	0.06	0.09	3.81	2.15
Esophagus	—	—	—	—	0.05	0.06	3.24	1.36
Stomach	0.07	0.04	4.81	0.97	0.12	0.18	7.76	4.32
Small intestine	0.02	0.02	1.32	0.59	0.05	0.07	3.12	1.65
Colon and rectum	0.07	0.14	4.45	3.41	0.05	0.07	3.01	1.75
Colon, except appendix	0.02	0.04	1.48	1.04	0.04	0.07	2.80	1.66
Colon, except rectum	0.02	0.04	1.66	0.88	0.04	0.07	2.80	1.66
Cecum	0.01	0.01	0.74	0.29	0.03	0.04	1.76	0.98
Appendix	0.03	0.02	1.91	0.42	0.05	0.07	3.17	1.72
Ascending colon	—	—	—	—	0.04	0.06	2.52	1.46
Hepatic flexure	—	—	—	—	0.04	0.06	2.83	1.53
Transverse colon	—	—	—	—	0.04	0.06	2.37	1.51
Splenic flexure	—	—	—	—	0.04	0.06	2.45	1.48
Descending colon	0.10	0.10	6.32	2.46	0.06	0.09	3.79	2.21
Sigmoid colon	0.04	0.10	2.79	2.41	0.05	0.09	3.61	2.32
Large intestine (colon), NOS	0.06	0.10	3.90	2.38	0.03	0.05	1.83	1.28
Rectum and rectosigmoid junction	0.14	0.20	9.21	4.85	0.05	0.08	3.50	1.99
Rectosigmoid junction	0.07	0.15	4.48	3.60	0.06	0.08	3.77	1.95
Rectum	0.15	0.20	9.96	4.99	0.05	0.08	3.37	2.02
Anus, anal canal, and anorectum	—	0.50	—	12.30	0.03	0.04	1.67	0.87
Liver and intrahepatic bile ducts	—	0.03	—	0.79	0.20	0.25	13.45	6.22
Liver	—	0.03	—	0.82	0.21	0.28	14.24	6.93
Gallbladder	0.75	—	49.75	—	0.06	0.10	3.85	2.55
Other biliary	0.38	—	24.88	—	0.08	0.12	5.63	2.83
Pancreas	0.02	0.07	1.44	1.64	0.04	0.07	2.95	1.74
Digestive tract, NOS	0.07	0.13	4.93	3.12	0.06	0.08	3.82	2.00
Peritoneum, omentum, and mesentery	—	—	—	—	0.05	0.04	3.15	0.95
Breast	—	—	—	—	0.04	0.07	2.59	1.62
Female genital system	—	0.06	—	1.49	0.04	0.06	2.50	1.50
Ovary	—	0.06	—	1.54	0.04	0.06	2.57	1.55
Other endocrine, induding thymus	—	0.07	—	1.64	0.09	0.13	6.18	3.23
Skin and soft tissue	—	—	—	—	0.02	0.02	1.02	0.44
Trachea, bronchi, lung	0.02	0.02	1.14	0.52	0.04	0.06	2.48	1.37

NOS: not otherwise specified.

[a] Population-corrected data were scaled by ratios as listed in Table 3.

the early SEER subset eclipse those in the subsequent period due, perhaps in part, to the high non-Asian: Asian citizen ratio in the 1980 United States Census data (Table 3). Interest in the apparent Asian propensity toward the development of carcinoid tumors should remain site-focused, because the overall Asian: non-Asian carcinoid ratio in the late SEER subset is 1.45, compared with a noncarcinoid ratio of 1.48 during the same period. Indeed, Asian:non-Asian ratios for the small intestine and appendix (0.59 and 0.42, respectively) may suggest a race-related protective effect for these sites.

Examination of similar data comparing Hispanic and non-Hispanic populations (Table 9) revealed no significantly elevated Hispanic:non-Hispanic carcinoid incidence ratio within the gastrointestinal or bronchopulmonary site groupings. In fact, these ratios, in most instances, are less than unity, suggesting the possibility of a genetic-based protective effect among the Hispanic population.

The crude male:female ratio previously reported for colonic carcinoids has dropped from 2.0 to 0.93 in the late SEER data set, whereas the male:female ratio for gastric carcinoids has fallen from 0.9 to 0.54 (Table 10). Male:female ratios for rectal carcinoids have remained steady at 1.05–1.11 over the past 30 years. The

TABLE 9
Hispanic:Non-Hispanic Ratios for Carcinoid and Noncarcinoid Tumors by Site: Third National Cancer Survey (1969–1971) and SEER (1973–1991) Registries

	Carcinoid tumors				Noncarcinoid tumors			
	Crude ratios		Corrected[a]		Crude ratios		Corrected[a]	
Carcinoid site	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999
All carcinoid sites	0.03	0.04	0.38	0.28	0.03	0.04	0.42	0.26
Digestive system	0.03	0.05	0.37	0.31	0.03	0.04	0.41	0.29
Esophagus	—	—	—	—	0.02	0.03	0.33	0.23
Stomach	0.04	0.10	0.59	0.64	0.05	0.07	0.76	0.47
Small intestine	0.03	0.03	0.39	0.23	0.03	0.03	0.41	0.21
Colon, except appendix	0.02	0.02	0.27	0.17	0.02	0.03	0.29	0.22
Colon and rectum	0.02	0.05	0.34	0.32	0.02	0.04	0.31	0.24
Colon, except rectum	0.02	0.03	0.23	0.17	0.02	0.03	0.29	0.22
Cecum	0.01	0.02	0.22	0.12	0.02	0.03	0.27	0.22
Appendix	0.01	0.03	0.19	0.17	0.03	0.04	0.49	0.24
Ascending colon	0.02	—	0.27	—	0.02	0.03	0.27	0.19
Hepatic flexure	—	0.17	—	1.12	0.02	0.03	0.25	0.19
Transverse colon	—	0.11	—	0.75	0.01	0.03	0.22	0.18
Splenic flexure	—	—	—	—	0.02	0.03	0.30	0.21
Descending colon	—	—	—	—	0.02	0.03	0.26	0.18
Sigmoid colon	0.03	0.04	0.45	0.28	0.02	0.04	0.34	0.26
Large intestine (colon), NOS	0.04	—	0.56	—	0.02	0.04	0.29	0.26
Rectum and rectosigmoid junction	0.04	0.06	0.52	0.41	0.02	0.04	0.36	0.29
Rectosigmoid junction	0.01	0.04	0.19	0.30	0.02	0.04	0.33	0.26
Rectum	0.04	0.06	0.57	0.42	0.03	0.04	0.38	0.30
Anus, anal canal, and anorectum	—	—	—	—	0.03	0.05	0.39	0.33
Liver and intrahepatic bile duct	—	0.19	—	1.24	0.05	0.08	0.73	0.54
Liver	—	0.15	—	0.99	0.05	0.09	0.75	0.57
Gallbladder	—	0.06	—	0.42	0.09	0.09	1.25	0.62
Other Biliary	0.10	—	1.45	—	0.04	0.05	0.58	0.34
Pancreas	—	—	—	—	0.03	0.04	0.47	0.27
Digestive tract, NOS	0.03	0.04	0.37	0.24	0.03	0.05	0.39	0.32
Peritoneum, omentum, and mesentery	—	—	—	—	0.03	0.05	0.50	0.31
Breast	—	—	—	—	0.03	0.04	0.37	0.24
Female genital system	0.05	—	0.67	—	0.05	0.06	0.66	0.39
Ovary	0.05	—	0.73	—	0.03	0.05	0.44	0.30
Testis	0.50	—	7.25	—	0.04	0.07	0.61	0.45
Other endocrine, including thymus	—	—	—	—	0.03	0.07	0.47	0.44
Skin and soft tissue	—	—	—	—	0.03	0.03	0.37	0.18
Trachea, bronchi, lung	0.03	0.03	0.44	0.23	0.02	0.03	0.27	0.17

NOS: not otherwise specified.
[a] Population-corrected data were scaled by ratios, as listed in Table 3.

female predominance of appendiceal carcinoids has decreased from 77% of the TNCS patients to 57% of the late SEER subgroup. The marked male predominance of noncarcinoid tumors of the trachea, bronchi, and lungs, however, decreased substantially during the same periods, with the male:female ratio dropping from 4.10 to 1.36.

As with the race-delineated statistics, correction of the raw patient numbers for actual population ratios can demonstrate either a deleterious effect or a protective gender effect. In carcinoids of the anal complex (anus, anal canal, and anorectum), the male:female incidence ratio is 2.08 times what would be expected if both the population ratio and the incidence rates for anal carcinoids were equivalent for males and females. Similar trends are noted for carcinoids of the descending colon and urinary system. However, male gender appears to impart a protective effect for carcinoids of the gallbladder, with a corrected male:female ratio of 0.32 in the late SEER subset; a similar but less pronounced gender disparity was noted for noncarcinoid tumors of the same site. This may suggest a relative gender-based propensity for carcinoid tumor

TABLE 10
Male:Female Ratios for Carcinoid and Noncarcinoid Tumors by Site: Third National Cancer Survey (1969–1971) and SEER (1973–1991) Registries

	Carcinoid tumors					Noncarcinoid tumors				
	Crude ratios			Corrected[a]		Crude ratios			Corrected[a]	
Carcinoid site	1969–1971	1973–1991	1992–1999	1973–1991	1992–1999	1969–1971	1973–1991	1992–1999	1973–1991	1992–1999
All carcinoid sites	—	0.81	0.82	0.85	0.86	—	0.90	0.96	0.95	0.99
Digestive system	—	0.90	0.99	0.94	1.03	—	1.10	1.12	1.17	1.17
Esophagus	—	—	0.50	—	0.52	—	2.49	2.84	2.63	2.95
Stomach	0.90	0.56	0.54	0.59	0.57	1.60	1.61	1.65	1.71	1.71
Small intestine	1.30	1.11	1.10	1.17	1.14	1.40	1.11	1.08	1.18	1.12
Colon and rectum	—	0.74	0.99	0.77	1.03	—	1.01	1.02	1.07	1.06
Colon, except appendix	2.00	0.68	0.93	0.72	0.96	0.90	0.93	0.94	0.98	0.98
Colon, except rectum	—	0.58	0.88	0.58	0.92	—	0.93	0.94	0.98	0.98
Cecum	—	0.49	0.68	0.53	0.71	—	0.77	0.80	0.82	0.83
Appendix	0.30	0.46	0.75	0.40	0.78	0.90	1.15	1.00	1.22	1.04
Ascending colon	—	0.72	0.93	0.75	0.97	—	0.83	0.82	0.88	0.85
Hepatic flexure	—	0.63	6.00	0.53	6.23	—	0.95	0.91	1.00	0.95
Transverse colon	—	0.50	1.00	0.53	1.04	—	0.81	0.83	0.86	0.86
Splenic flexure	—	0.80	1.00	0.85	1.04	—	1.16	1.12	1.23	1.17
Descending colon	—	1.30	2.25	1.38	2.34	—	1.02	1.15	1.08	1.20
Sigmoid colon	—	1.06	1.16	1.15	1.21	—	1.08	1.12	1.15	1.17
Large intestine (colon), NOS	—	1.03	1.12	1.06	1.16	—	0.80	0.90	0.85	0.93
Rectum and rectosigmoid junction	—	1.06	1.05	1.12	1.09	—	1.24	1.27	1.32	1.32
Rectosigmoid junction	—	0.78	1.06	0.86	1.10	—	1.17	1.23	1.23	1.28
Rectum	1.10	1.11	1.05	1.17	1.09	1.20	1.29	1.28	1.36	1.33
Anus, anal canal, and anorectum	—	1.25	2.00	1.32	2.08	—	0.63	0.85	0.67	0.89
Liver and intrahepatic bile ducts	—	0.75	1.91	0.79	1.98	—	1.93	2.03	2.05	2.11
Liver	—	0.75	1.82	0.79	1.89	—	2.05	2.33	2.18	2.42
Gallbladder	—	0.40	0.31	0.42	0.32	—	0.37	0.44	0.40	0.46
Other biliary	—	1.20	1.00	1.06	1.04	—	1.04	1.06	1.10	1.10
Pancreas	—	1.47	1.00	1.50	1.04	—	1.02	0.94	1.08	0.98
Digestive tract, NOS	—	1.38	1.00	1.47	1.04	—	0.90	0.94	0.95	0.98
Peritoneum, omentum, and mesentery	—	1.00	0.86	1.06	0.89	—	0.73	0.25	0.78	0.26
Urinary system	—	2.00	3.00	2.12	3.12	—	2.37	2.26	2.50	2.34
Other endocrine, induding thymus	—	3.17	3.00	3.18	3.12	—	1.21	1.09	1.28	1.14
Trachea, bronchi, lung	0.80	0.65	0.51	0.69	0.53	4.10	2.06	1.36	2.18	1.41

NOS: not otherwise specified.

[a] Population-corrected data were scaled by ratios as listed in Table 3.

development at the gallbladder. Similarly, although the male:female ratio for noncarcinoid tumors of the tracheobronchopulmonary complex was 1.41, the population-corrected ratio for carcinoid tumors at the same site was only 0.53 within the late SEER subset. This suggests that although males are more likely than females to develop a noncarcinoid tumor at this site, females are almost twice as likely as males to develop a bronchopulmonary carcinoid tumor.

Age-Adjusted Incidence

To evaluate the possibility that gender and race differences may remain obscured in the unadjusted tabulation (Table 6), age-adjusted incidence rates were calculated for data from the early SEER and late SEER subsets (Table 11). Rates are expressed as the number of patients per 100,000 population per year. The age-adjusted incidence rates of carcinoid tumors were compiled by site, gender, and race; and the results were compared with the results from the TNCS file, as presented previously.

In general, incidence rates were higher in the black population, with the exception of appendiceal carcinoids and bronchopulmonary carcinoids. The age-adjusted incidence rates for appendiceal carcinoids decreased across all gender and race divisions, whereas the age-adjusted incidence rates for bronchopulmonary carcinoids has increased over the past 30 years within each race and gender subgrouping. Changes in the latter may reflect the increased use of fiber-optic bronchoscopy and biopsy with subsequent increases in carcinoid identification. However, no

TABLE 11
Age-Adjusted Incidence Rates of Carcinoid Tumors by Site, Race, and Gender: Third National Cancer Survey (1969–1971) and SEER (1973–1999) Registries[a]

	White males			White females			Black males			Black females		
Carcinoid site	**1969–1971**	**1973–1991**	**1992–1999**	**1969–1971**	**1973–1991**	**1992–1999**	**1969–1971**	**1973–1991**	**1992–1999**	**1969–1971**	**1973–1991**	**1992–1999**
All carcinoid sites	1.31	1.33	2.47	1.63	1.40	2.58	2.16	2.28	4.48	1.87	1.77	3.98
Digestive system	—	0.84	1.77	—	0.79	1.49	—	1.84	3.91	—	1.22	3.13
Stomach	0.03	0.03	0.12	0.02	0.05	0.18	0.10	0.09	0.25	0.10	0.08	0.24
Small intestine	0.48	0.47	0.88	0.28	0.34	0.63	0.82	0.89	1.65	0.52	0.44	1.15
Colon and rectum	—	0.30	0.68	—	0.37	0.60	—	0.80	1.91	—	0.66	1.61
Colon, except appendix	0.11	0.11	0.21	0.07	0.13	0.18	0.15	0.23	0.38	0.07	0.20	0.28
Colon, except rectum	—	0.18	0.27	—	0.26	0.26	—	0.30	0.47	—	0.30	0.32
Cecum	—	0.05	0.09	—	0.08	0.10	—	0.07	0.13	—	0.10	0.13
Appendix	0.25	0.06	0.06	0.79	0.13	0.08	0.14	0.08	0.08	0.61	0.12	0.03
Ascending colon	—	0.01	0.02	—	0.01	0.01	—	0.02	0.01	—	0.01	0.03
Hepatic fiexure	—	0.00	0.01	—	—	—	—	—	—	—	0.01	—
Transverse colon	—	0.01	0.01	—	0.01	0.01	—	—	—	—	0.01	—
Splenic flexure	—	—	—	—	—	—	—	0.01	—	—	—	—
Descending colon	—	0.01	0.01	—	—	—	—	0.02	0.03	—	0.01	0.01
Sigmoid colon	—	0.02	0.05	—	0.02	0.04	—	0.09	0.20	—	0.04	0.10
Large intestine (colon), NOS	—	0.01	0.02	—	0.01	0.02	—	0.02	0.01	—	0.02	0.01
Rectum and rectosigmoid junction	—	0.12	0.41	—	0.10	0.35	—	0.50	1.44	—	0.35	1.29
Rectosigmoid junction	—	0.01	0.04	—	0.02	0.04	—	0.07	0.22	—	0.06	0.12
Rectum	0.14	0.10	0.38	0.15	0.09	0.31	0.76	0.43	1.22	0.28	0.29	1.17
Liver	—	—	0.02	—	—	0.01	—	—	0.03	—	—	0.03
Gallbladder	—	—	0.01	—	—	0.01	—	—	—	—	—	0.02
Other biliary	—	—	0.01	—	—	0.01	—	—	0.02	—	0.01	0.00
Pancreas	—	0.02	0.02	—	0.01	0.01	—	0.02	0.02	—	0.03	0.04
Digestive tract, NOS	—	0.02	0.06	—	0.03	0.06	—	0.11	0.26	—	0.07	0.15
Ovary	—	—	—	—	0.02	0.06	—	—	—	—	0.03	0.11
Other endocrine, including thymus	—	0.01	0.01	—	—	—	—	—	0.01	—	—	—
Trachea, bronchi, lung	0.22	0.38	0.52	0.24	0.50	0.89	0.15	0.32	0.39	0.06	0.37	0.57

NOS: not otherwise specified.

[a] Rates are per 100,000 population per year.

clear explanation of the changes noted for appendiceal carcinoid data is available. The rates for gastric carcinoids increased in all groups between the TNCS data set and the late SEER data set, as have the rates for colonic carcinoids; increases in incidence for the latter have been between 150% and 300% among black males and females, respectively. Among the white population (both male and female), the highest rates were noted for small intestinal carcinoids (male, 0.88; female, 0.63) and bronchopulmonary carcinoids (male, 0.52; female, 0.89). In addition, in the black population (both male and female), a high incidence of rectal carcinoids was observed, with rates rising to 1.22 and 1.17 per 100,000 population per year, respectively, in the late SEER subset.

Associated Neoplasms

The SEER database facilitates the identification of patients with carcinoid tumors who are diagnosed with additional carcinoid or noncarcinoid tumors. Across all anatomic sites, 22.4% of carcinoid tumors in the late SEER subset were associated with other (noncarcinoid) neoplasms (data not presented). Within this period (1992–1999), it was noted that a high percentage of associated tumors occurred with small intestinal carcinoids (29.0%), whereas lower rates were found with rectal, gallbladder, appendiceal, and pancreatic carcinoids (13.1%, 17.6%, 18.2%, and 18.8%, respectively). However, because these groups represent a relatively small number of patients, the accuracy of the latter observation is questionable.

Although patients with gastric carcinoid tumors had an increased incidence of additional noncarcinoid tumors in the pan-SEER data set compared with the ERG and TNCS groups (20.5–27.8% vs. 14% and 5%, respectively), this rate decreased by 26% between the early SEER and late SEER subsets. This may represent recent improvements in endoscopic screening, biopsy, and identification of carcinoid tumors over the past decade. It is possible that removal of carcinoid tumors lessens the incidence of associated tumors, because carcinoids, left undisturbed, may continue to produce proliferative peptides, enhancing the development or growth of other neoplasia. There is some speculation regarding the pericarcinoid micromilieu, which may promote the development of gastric adenocarcinomata.[19] Similar improvements in colonoscopy surveillance, with early carcinoid nodule identification, may explain the overall decrease of 16% in tumors associated with colorectal carcinoids.

Metastatic Dissemination

The distribution of the SEER data by site and stage was examined to evaluate the propensity of individual sites of carcinoid tumors to develop regional or distant metastases; comparison to earlier data was made with the ERG series. Disparate percentages of lesions (0.5% and 14.6%) of the ERG series and the late SEER series, respectively, had not been staged. For the late SEER period, this may be attributed to documentation mandated by many hospitals at the time of patient discharge that requests the recording of tumor staging; this information may not always be available promptly; as such, tumors in these patients automatically may be designated as unstaged, even though this information subsequently becomes available. To determine the range of frequencies at presentation for nonlocalized carcinoid tumors, unstaged lesions were included serially within both localized and nonlocalized groupings; these results are presented in Table 12. The most significant variances are observed within carcinoids of the liver, stomach, and rectum (unstaged lesions in 32.3%, 22.9%, and 14.4% of patients, respectively). The percentage of nonlocalized gastric lesions decreased over the past 49 years from 55% (ERG) to 30.1% (early SEER). A further decrease to 9.6% in the late SEER subset is evident despite the overall increase in incidence of gastric carcinoids (Table 4). This may reflect an earlier stage diagnosis facilitated by increased utilization of upper gastrointestinal endoscopy and biopsy.

Overall, sites with the greatest percentages of nonlocality at the time of presentation in the late SEER data set included the cecum, pancreas, and small intestine (81.5%, 71.9%, and 58.3%, respectively). Nonlocalized appendiceal carcinoids, which comprised only 5% of all appendiceal carcinoids within the ERG data set, as noted previously, were increased to at least 38.8%. This may represent improved awareness of the biology of the lesion or greater sampling of periappendiceal lymph nodes and surrounding tissues at appendectomy. Cumulative analysis of all types of carcinoid tumors in the SEER group indicated that in 12.9% of patients, metastases already were evident at the time of diagnosis. This suggests that widely held beliefs regarding the benignity of carcinoid tumors should be revised and made clear to both the public and practitioners.

Five-Year Survival Rates

The 5-year survival rates of carcinoid tumors were tabulated by site and extent. In nearly all carcinoid tumors, irrespective of site, the stage of the disease closely paralleled overall survival (Table 13). The 5-year survival rate for all types of carcinoid tumor across all stages within the late SEER subset was 67.2%, a modest increase compared with the early SEER subset (59.5%). The presence of regional and

TABLE 12
Distribution of Carcinoid Tumors by Site and Stage, With and Without Superlocalization Staging: End Results Group (1950–1969) and SEER (1973–1999) Registries

	Localized %[a]			Regional %			Distant %			Unstaged %			Nonlocalized %		
Carcinoid site	**1950–1969**	**1973–1991**	**1992–1999**	**1950–1969**	**1973–1991**	**1992–1999**	**1950–1969**	**1973–1991**	**1992–1999**	**1950–1969**	**1973–1991**	**1992–1999**	**1950–1969**	**1973–1991**	**1992–1999**
All carcinoid sites	74.1	44.4	53.3	13.4	23.7	19.2	11.4	18.5	12.9	0.5	13.4	14.6	25	42.2–55.6	32.1–46.7
Digestive system	—	38.3	52.7	—	28.2	20.9	—	25.7	15.5	—	7.8	11.0	—	53.9–61.7	36.3—47.3
Stomach	45.2	51.7	67.5	28.6	10.0	3.1	23.8	20.1	6.5	2.4	18.2	22.9	55	30.1–48.3	9.6–32.5
Small intestine	40.1	25.0	35.9	30.8	38.7	35.9	28.9	31.3	22.4	0.3	4.9	5.8	60	70.1–75.0	58.3–64.1
Colon and Rectum	—	52.3	67.3	—	20.5	10.2	—	18.4	9.5	—	8.8	13.0	—	38.9–47.7	19.7–32.7
Colon, except appendix	29.2	21.5	33.4	36.3	31.7	25.8	33.6	38.2	29.5	0.9	8.6	11.3	71	69.9–78.5	55.3–66.6
Colon, except rectum	—	38.4	38.7	—	29.7	26.5	—	26.0	24.8	—	5.9	10.0	—	55.8–61.6	51.3–61.3
Cecum	—	12.5	16.8	—	40.6	40.5	—	43.9	41.0	—	3.0	1.7	—	84.5–87.5	81.5–83.2
Appendix	95.5	62.1	55.4	3.8	26.9	28.9	0.7	9.0	9.9	0	2.0	5.8	5	35.9–37.9	38.8–44.6
Sigmoid colon	—	55.4	71.7	—	13.9	4.7	—	19.8	6.6	—	10.9	17.0	—	33.7–44.6	11.3–28.3
Large intestine (colon), NOS	—	1.7	16.7	—	6.8	2.8	—	49.2	30.6	—	42.4	50.0	—	55.9–98.3	33.3–83.3
Rectum and rectosigmoid junction	—	73.1	81.3	—	6.8	2.3	—	6.9	2.0	—	13.2	14.5	—	13.7–26.9	4.2–18.7
Rectosigmoid junction	—	61.3	77.3	—	12.5	3.1	—	12.5	4.1	—	13.8	15.5	—	25.0–38.8	7.2–22.7
Rectum	85.1	74.8	81.7	6.4	5.9	2.2	8.1	6.1	1.7	0.3	13.1	14.4	15	12.1–25.2	3.9–18.3
Anus, anal canal, and anorectum	—	33.3	88.9	—	22.2	—	—	22.2	11.1	—	22.2	—	—	44.4–66.7	11.1–11.1
Liver		50.0	35.5	—	—	29.0		28.6	3.2		21.4	32.3		28.6–50.0	32.3–64.5
Gallbladder		14.3	82.4	—	42.9	5.9		28.6	11.8		14.3	—		71.4–85.7	17.6–17.6
Pancreas		8.5	18.8	—	12.8	12.5		61.7	59.4		17.0	9.4		74.5–91.5	71.9–81.3
Digestive tract, NOS	26.3	44.3	60.7	15.8	13.7	9.0	47.4	28.2	15.2	10.5	13.7	15.2	74	42.0–55.7	24.1–39.3
Peritoneum, omentum and mesentery	—	25.0	30.8	—	25.0	46.2	—	25.0	15.4	—	25.0	7.7	—	50.0–75.0	61.5–69.2
Female genital system	—	62.2	67.1	—	4.4	7.1	—	31.1	21.4	—	2.2	4.3	—	35.6–37.8	28.6–32.9
Ovary		64.3	67.6	—	2.4	5.9		31.0	22.1		2.4	4.4		33.3–35.7	27.9–32.4
Other endocrine, including thymus	—	20.0	18.8	—	20.0	37.5	—	56.0	12.5	—	4.0	31.3	—	76.0–80.0	50.0–81.3
Trachea, bronchi, lung	79.1	66.1	65.4	15.2	19.3	5.2	6.9	8.2	0.5	6.7	7.1	21		27.2–33.9	27.5–34.6

NOS: not otherwise specified.

[a] Includes tumors registered as in situ.

TABLE 13
Five-Year Survival Rate of Patients with Carcinoid Tumors by Site and Stage: SEER (1973–1999) Registry

	Localized %		Regional %		Distant %		Unstaged %		All stages %[a]	
Carcinoid site	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999
All carcinoid sites	77.5	78.2	63.1	71.7	26.7	38.5	39.3	48.3	59.5 ± 0.6	67.2 ± 0.9
Digestive system	72.7	76.3	60.7	69.4	28.6	40.9	58.0	62.4	56.7 ± 0.8	67.5 ± 1.1
Stomach	64.5	69.1	38.1	—	7.1	21.2	70.3	64.7	51.2 ± 3.5	63.0 ± 3.6
Small intestine	53.7	59.9	64.1	72.8	36.1	50.0	46.3	32.9	51.9 ± 1.2	60.5 ± 1.7
Colon and rectum	84.7	87.3	56.8	68.5	21.2	29.7	64.5	83.1	65.2 ± 1.2	78.4 ± 1.4
Colon, except rectum	85.7	76.0	58.8	71.6	21.7	30.0	58.8	71.8	59.1 ± 1.6	61.8 ± 2.8
Cecum	55.9	78.5	54.6	78.0	31.1	43.6	50.0	—	44.3 ± 3.0	61.0 ± 4.6
Appendix	92.3	80.8	81.3	88.1	30.6	9.6	62.5	66.7	83.0 ± 1.9	71.0 ± 5.9
Descending colon	85.7	80.0	40.0	50.0	—	—	—	100.0	43.5 ± 10.3	68.4 ± 15.1
Sigmoid colon	86.8	75.1	28.6	—	5.0	—	70.0	84.8	60.2 ± 4.9	70.9 ± 5.7
Large intestine (colon), NOS	—	—	50.0	—	13.8	28.7	57.1	71.9	33.3 ± 6.4	59.3 ± 9.9
Rectum and rectosigmoid junction	83.9	89.9	44.2	49.0	18.2	25.8	68.2	87.1	74.4 ± 1.8	87.1 ± 1.4
Rectosigmoid junction	83.2	80.9	70.0	—	10.0	—	60.0	83.3	69.3 ± 5.2	76.7 ± 5.6
Rectum	84.0	90.8	36.4	48.9	20.6	32.3	69.5	87.4	75.2 ± 1.9	88.3 ± 1.4
Anus, anal canal, and anorectum	33.3	100.0	100.0	—	—	—	50.0	—	44.4 ± 16.6	100.0 ± 0.0
Liver	14.3	—	—	16.2	—	—	33.3	20.0	14.3 ± 9.4	18.4 ± 8.9
Gallbladder	—	75.7	33.3	—	—	—	—	—	14.3 ± 13.2	58.8 ± 13.3
Other biliary	83.3	60.0	20.0	86.7	—	—	—	—	54.6 ± 15.0	60.8 ± 14.8
Pancreas	75.0	63.6	16.7	—	24.1	40.9	62.5	—	34.0 ± 6.9	37.5 ± 10.1
Other digestive organs	—	—	100.0	—	12.0	—	20.0	50.0	16.1 ± 6.6	16.0 ± 10.0
Peritoneum, omentum, and mesentery	100.0	—	—	—	—	—	100.0	—	50.0 ± 25.0	—
Breast	55.6	—	100.0	100.0	33.3	—	—	—	57.1 ± 13.2	66.7 ± 27.2
Urinary system	100.0	100.0	—	—	—	—	—	—	33.3 ± 27.2	100.0 ± 0.0
Female genital system	96.4	91.4	50.0	—	7.1	28.3	100.0	100.0	66.5 ± 7.1	75.2 ± 7.2
Ovary	96.3	90.9	100.0	—	7.7	28.3	100.0	100.0	68.9 ± 7.2	74.1 ± 7.5
Male genital system	80.0	100.0	—	—	—	—	—		71.4 ± 17.1	100.0 ± 0.0
Testis	100.0	100.0	—	—	—	—	—	—	100.0 ± 0.0	100.0 ± 0.0
Other endocrine, including thymus	60.0	100.0	40.0	100.0	28.6	50.0	—	60.0	36.0 ± 9.6	79.5 ± 10.6
Trachea, bronchi, lung	82.8	81.1	69.8	76.7	14.6	25.6	56.5	47.5	73.7 ± 1.1	73.5 ± 1.5

NOS: not otherwise specified.
[a] Values shown are the means ± standard error.

distant metastases (as may be predicted) was associated with a significant worsening in prognosis, as reflected by the survival rates (71.7% and 38.5%, respectively). Unstaged lesions overall had a 48.3% 5-year survival rate, possibly suggesting that the majority of such unstaged tumors behaved similarly to tumors with regional or distant spread.

The correlation between the extent of the disease and crude survival for the ERG database provided by Godwin[18] is not directly comparable with those in the SEER database, because only relative survival rates were reported in the previous study. The relative survival rate is the ratio of the observed survival rate for the affected patient group to the expected survival rate for similar, nonaffected persons in the general population[11]; this ratio indicates the probability that patients will survive the effects of disease and, in fact, will escape death due to causes associated with their malignancy and will perish instead from factors such as heart disease, accidents, and diseases of old age. The relative survival rate, therefore, always is greater than the observed survival rate for the same group of patients.

Godwin reported the 5-year relative survival rates for patients with carcinoid tumors in the ERG database (localized, 94%; regional, 64%; distant, 18%; all stages, 82%).[18] Because relative survival rates always are greater than observed survival rates for the same patient cohort, there is an apparent increase in the survival of patients with nonlocalized carcinoids from the SEER series compared with the ERG series.

In 1963, Williams and Sandler[15] classified carcinoids according to their histology and anatomic site of origin: 1) foregut carcinoids (respiratory tract, stomach, duodenum, biliary system, and pancreas), 2) midgut carcinoids (small bowel, appendix, cecum, and proximal colon), and 3) hindgut carcinoids (distal colon and rectum). Querying the SEER database with these three groupings revealed overall 5-year survival rates of 69.6%, 60.8%, and 88.3%, respectively (Table 14). Because 41–49% of colonic carcinoids occurred proximal to the midtransverse colon (the putative border between the midgut and the hindgut) (Table 5), analysis of the data attributing all colonic lesions as midgut carcinoids was performed. If small intestinal and appendiceal lesions alone were grouped as midgut carcinoids, and if all nonappendiceal colonic and rectal lesions were grouped as hindgut carcinoids, then the 5-year survival rates were 61.3% for patients with carcinoids of the midgut and 79.0% for patients with carcinoids of the hindgut. If bronchopulmonary carcinoids are excluded from the foregut group, as defined above, then the 5-year survival rate falls to 56.2%. Defense of these groupings on biologic grounds may be flawed, however, because the precise cell type of origin of the neuroendocrine tumor in each organ needs to be identified rather than basing a prediction on an organ site alone.

Overall, the best 5-year survival rate was noted for patients with rectal, appendiceal, and bronchopulmonary carcinoids (88.3%, 71.0%, and 73.5% for all stages, respectively, within the late SEER group). These values correspond with the analysis of the ERG series by Godwin.[10] In the current series, patients with hepatic and pancreatic carcinoids exhibited poor overall survival (18.4% and 37.5%, respectively).

DISCUSSION

Carcinoids, as the most frequently occurring neuroendocrine tumors,[20] have long been thought mostly benign. However, it has been shown that these neoplasms often exhibit a malignant clinical course. Unfortunately, the criteria for establishing the degree of malignancy in carcinoid tumors remain unclear; histologic analysis often fails to distinguish precisely the likelihood of aggressive or metastatic potential. Sadly, even at this juncture (a century after the original histologic observation of Oberndorfer), the size of the primary tumor most often is cited as the critical determinant in the prediction of biologic behavior. However, recent reports note that the malignant potential of even the smallest lesions should not be overlooked.[21] Although studies have suggested that proliferation markers, such as Ki-67 and proliferating cell nuclear

TABLE 14
Five-Year Survival Rates from the SEER Registry for Patients with Carcinoid Tumors of the Foregut, Midgut, and Hindgut Based on Original and Modified Williams and Sandler Classifications[a]

Carcinoid site	Localized %		Regional %		Distant %		Unstaged %		All stages %	
	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999	1973–1991	1992–1999
Foregut (stomach, liver, gallbladder, pancreas, trachea, bronchi, lung)	80.8 ± 1.1	78.3 ± 1.6	67.0 ± 2.4	71.2 ± 3.5	13.9 ± 2.5	26.5 ± 4.5	59.1 ± 3.8	50.6 ± 5.1	69.8 ± 1.0	69.6 ± 1.4
Foregut (gastrointestinal sites only)	61.3 ± 4.5	67.5 ± 4.0	33.3 ± 8.6	10.9 ± 9.6	13.0 ± 3.8	28.5 ± 8.3	65.3 ± 6.8	53.1 ± 7.0	45.5 ± 3.0	56.2 ± 3.3
Midgut (small intestine, appendix, colon)	68.2 ± 1.7	64.2 ± 2.4	62.5 ± 1.6	72.5 ± 2.4	31.5 ± 1.7	44.1 ± 3.0	51.1 ± 4.3	47.6 ± 5.5	54.4 ± 1.0	60.8 ± 1.5
Midgut (small intestine, appendix)	67.5 ± 1.8	62.2 ± 2.6	66.4 ± 1.7	73.5 ± 2.6	35.7 ± 2.0	48.2 ± 3.6	47.8 ± 5.3	34.6 ± 6.8	57.6 ± 1.1	61.3 ± 1.6
Hindgut (rectum)	84.0 ± 1.9	90.8 ± 1.4	36.4 ± 8.4	48.9 ± 17.3	20.6 ± 6.9	32.3 ± 15.7	69.5 ± 5.7	87.4 ± 4.0	75.2 ± 1.9	88.3 ± 1.4
Hindgut (colon, except appendix, with rectum)	81.5 ± 1.6	87.8 ± 1.5	45.5 ± 3.4	64.1 ± 5.5	19.8 ± 2.5	31.7 ± 4.8	64.6 ± 4.4	83.8 ± 3.5	59.3 ± 1.4	79.0 ± 1.4

[a] Values shown are means ± standard error.

antigen, may be of use,[22,23] the best aggregate indicators of prognosis and malignancy appear to be evidence of invasive growth and the presence of regional or distant metastases.

The distribution of carcinoid tumors across various anatomic sites is worthy of close examination. These lesions often are incidental findings and, thus, their relative incidence certainly will increase as screening techniques and indications are broadened.[24] Furthermore, the detection rate for carcinoid tumors may be biased by the group sampled. This is exemplified best by the report of Berge and Linell,[25] who evaluated 16,294 autopsies and 44 surgical specimens in Malmo between 1958 and 1969, noting a carcinoid incidence of 8.4 per 100,000 population per year, which is nearly twice the age-adjusted incidence in the late SEER group recorded in the most affected United States group, the black male population (4.48 per 100,000 population per year) (Table 11). This discrepancy with the autopsy-based series described above suggests that considerable percentages of carcinoid tumors remain asymptomatic and undetected during life.

Recent incidence rates for all types of carcinoid tumors in Sweden have been estimated by Hemminki and Li at 2.0 for men and 2.4 for women, based on a subset of 5184 tumors examined between 1958 and 1998.[26] These data are comparable to the results found in the current study (Table 11). Other groups have reported somewhat lower incidence rates. In a series of 3382 carcinoid tumors of all types in England, Newton et al. reported an overall age-adjusted incidence of 0.71 for men and 0.87 for women per 100,000 population per year.[27] The Tuscany Tumor Registry, as noted by Crocetti et al.,[28] suggests a carcinoid incidence rate of 0.65. Incidence rates for both men and women in Denmark are around 1.1 per 100,000 person-years.[29]

Stomach

The percentage of gastric carcinoids among all carcinoid tumors increased from 2.25% in Godwin's series[10] to 5.85% in the late SEER subset (Table 4) and remains at 4.10% of the entire set of 13,715 carcinoid tumors. In the series by Berge and Linell, gastric carcinoids comprised 2.9% of 244 carcinoid tumors of all types.[25] In a later series, Levi et al.[30] analyzed 248 carcinoid tumors registered from 1974 to 1989 in canton Vaud of Switzerland and noted a 4.2% relative percentage for gastric carcinoids in males and 4.6% in females. It is also apparent that the percentage of gastric carcinoids in relation to all gastric tumors also has been increasing (TNCS, 0.3%; SEER 1973–1987, 0.4%;[15] early SEER, 0.55%; late SEER, 1.77%). Whether this represents a true increase or a change in reporting (the 501 gastric carcinoid tumors recorded in the SEER registry significantly overshadow the 61 tumors accrued prior to 1973) or whether it is the result of increased awareness and the employment of modern diagnostic modalities, such as endoscopy and immunohistochemistry, remains unclear.

The association between hypergastrinemia associated with low-acid states and gastric enterochromaffin-like (ECL) cell hyperplasia and subsequent neoplasia has been demonstrated in both human and animal models.[31–33] Gastric carcinoid tumors have not been identified specifically in association with long-term acid-inhibitory therapy, although ECL cell hyperplasia has been observed in such individuals.[34–37] It is particularly interesting to note the proposed relation between gastric adenocarcinoma and gastric carcinoids.[38–42] It has been hypothesized that carcinoid lesions arising from a low-acid state may promote alterations in adjacent mucosal cells through the secretion of various growth factors, eventually culminating in the formation of adenocarcinomata.[43] Although this has not been proven to date, the predominance of gastric carcinoids in females and in the black and Asian populations suggests the possibility of a hormonal or genetic predisposition to such disease. Support is found in the increased incidence of gastric carcinoids associated with gastrinomas of the multiple endocrine neoplasia syndrome, type 1 (MEN-1), but not with sporadic gastrinomas.[33] A similar genetic propensity has been noted in an African rodent model of gastric carcinoid.[44]

Although the majority of gastric carcinoid tumors are recognized at an early stage and demonstrate a good prognosis, the modest 63.0% all-stage, 5-year survival rate demonstrates that such lesions may exhibit significantly malignant behavior. The inclusion of nonenterochromaffin-like cell lesions, which are gastrin-independent and have a far worse prognosis, may have an adverse influence on the more benign prognosis usually accorded to this group. It may have been predicted that, with the changes in reporting strategy incorporated in 1986 (i.e., all carcinoids not otherwise identified subsequently were designated malignant and, thus, reportable), the inclusion of lesions previously considered benign may result in a shift toward an increased percentage of localized disease; there is insufficient evidence for confirmation of this prediction. It is possible either that more aggressive forms of gastric carcinoids exist or that more zealous diagnostic sampling is increasing the yield of nonlocalized disease.

Small Intestine

Small bowel carcinoids currently are the most frequently occurring type of carcinoid tumors (25.2% of all carcinoids among all 13,715 tumors and 28.5% of the pan-SEER data set). The predominance of this site has been noted by others.[27,45,46] Gabos et al.[47] analyzed 1244 small intestinal carcinomas registered between 1975 and 1989 in western Canada and noted that carcinoids comprised 26.8% of such lesions and represented the second most frequent neoplasm encountered in the small intestine after adenocarcinoma. DiSario and associates[48] evaluated 328 small bowel tumors that were identified in the Utah Cancer Registry from 1966 through 1990 (most of which are included in the SEER registry) and noted that carcinoids comprised 41% of all lesions at this site, whereas adenocarcinoma was diagnosed in 24% of such patients. Within the late SEER data set, carcinoids comprised 43.5% of all small intestinal tumors. It appears that the biology of the small intestine is not as a single organ but, instead, exhibits a graduated propensity for developing neuroendocrine neoplasia along its longitudinal axis. Indeed, the majority of previously identified duodenal carcinoids are classified now as gastrinomas. It is likely that the specific endocrine cell types in each region of the small intestine give rise to distinct species of carcinoid tumors; in many instances, the specific biology of these lesions remains unclear.[49] Although carcinoids in the late SEER group comprised just over 40% of all small intestinal primary tumors, in the autopsy series by Berge and Linell, this number was 95%, with 88% of such lesions identified as incidental findings.[25] This clearly demonstrates that the evaluation of autopsy series may significantly alter many aspects of epidemiology data and further emphasizes the growing body of evidence that many carcinoid lesions remain asymptomatic and undetected in vivo. Within the late SEER population, the age-adjusted incidence rate (expressed as cases per 100,000 population per year) for small intestinal carcinoids (Table 11) is high in the black male population (1.65) compared with black females (1.15), white males (0.88), and white females (0.63). DiSario et al.[48] reported a 0.8 per 100,000 population per year, age-adjusted incidence in males and a 0.5 per 100,000 population per year incidence in females for these lesions. In the current SEER registry, the crude male: female ratios for small intestinal carcinoids and noncarcinoid tumors (Table 10) were nearly equivalent (1.10 and 1.08, respectively), although DiSario et al. noted a higher male:female ratio for carcinoids (1.6) and an even higher male:female ratio for noncarcinoids (2.0) at this site. The changes in registry reporting techniques in 1986 appear to have had little or no effect on overall frequency, site, and stage distribution of small intestine lesions compared with a later SEER subset analysis.[15] This may reflect the observation that small bowel carcinoids more often are malignant; thus, almost all such tumors already were being reported to SEER registries prior to the 1986 change in protocol.

Other noncarcinoid neoplasms are associated overtly with small bowel carcinoids in 29% of patients. This is the largest percentage association among all extrahepatic gastrointestinal carcinoid sites and supports the hypothesis that the cells of origin of such lesions may exhibit the highest propensity for the production of growth factors.[8]

At the time of diagnosis, 58–64% of patients with small intestine carcinoids had nonlocalized disease, compared with an overall percentage of 32–46% off all patients with gastrointestinal carcinoids (Table 12). Saha et al. reported a series of 112 gastrointestinal carcinoids that were identified in a New Orleans hospital during a 44-year period in which 10% of 40 patients with small intestinal carcinoids died of liver metastases.[50] In an analysis of 192 patients with gastrointestinal carcinoids who were treated at the University of Iowa between 1938 and 1982, Olney and colleagues[51] noted that 32.9% of 79 small intestinal lesions exhibited metastatic disease and that this frequency was the highest (40%) for the ileal carcinoid subset. In the autopsy series by Berge and Linell, it was noted that 28.3% of 152 small intestinal carcinoid tumors had metastasized.[25]

In the late SEER database, the 5-year survival rate for patients with small intestinal carcinoid tumors was 60.5%, compared with the overall percentage of 67.2% for patients with all gastrointestinal carcinoids (Table 13). This is somewhat better compared with the 30–33% 5-year survival rate reported in the New Orleans and Iowa series.[50,51]

Meckel Diverticulum

To our knowledge to date, only 109 diagnoses of carcinoids arising within a Meckel diverticulum have been reported in the literature, and, in the SEER group, 52 such lesions have been encountered.[52–55] Moyana reported a series of 44 surgical specimens of Meckel diverticula in which 9% ($n = 4$ specimens) harbored a carcinoid tumor.[56] The mean age of these patients was 57 years, and they had a survival rate of 100% after a mean follow-up of 10.2 years. Moyana noted that the immunohistochemical profile of Meckelian carcinoids is similar to that of small intestinal carcinoids. Nies et al.[52] analyzed two of their own patients with carcinoid tumors within Meckel diver-

ticula along with an additional 104 patients reported in the literature; these authors reported that 64.4% of such carcinoids were asymptomatic and that 25.5% were incidental findings at autopsy. In that series, the average age at diagnosis was 56.8 years. Those authors also stated that metastases were present in 24% of patients at the time of presentation. It is noteworthy that Nies et al. found a 2.6 male:female ratio. The propensity of such lesions to occur in blind diverticula of the gut suggests that alterations in luminal content may be of significance. This is supported by the observation that the incidence of gastric carcinoids is increased when gastric pH is elevated either in experimental models or in patients with atrophic gastritis or pernicious anemia.[43]

Appendix

Although appendiceal carcinoids have long been recognized as the most frequently occurring carcinoid tumors, their relative frequency, reflected by the three registries examined herein, has decreased over time (ERG, 43.9%; TNCS, 35.5%; late SEER, 2.43%) (Table 4). However, this information should be evaluated and interpreted cautiously, because the ERG file contains both benign and malignant appendiceal carcinoids, whereas the TNCS and the initial 14-year period of SEER case accrual do not. An alternative explanation for this apparent decrement is the somewhat relaxed surgical commitment to appendectomy over the past 2 decades. Addiss et al.[57] reported an analysis of the files of the United States National Hospital Discharge Survey between 1970 and 1984, noting that the overall incidence of primary appendectomy decreased by 22.1%, whereas diagnostic accuracy (appendicitis rate ÷ primary appendectomy rate) increased from 74% to 83% in females and from 86% to 92% in males.

The relative frequency of appendiceal carcinoids, compared with all appendiceal malignancies, has decreased within the SEER registry over time. During 1973–1987, 376 patients with appendiceal carcinoids were reported, comprising 40% of all appendiceal malignancies.[15] In contrast, the pan-SEER file (1973–1999) contains 519 patients with appendiceal carcinoids, comprising only 25.3% of all appendiceal malignancies (Tables 4,7). The marked female predominance for small bowel carcinoids evident in these three series also was noted by Roggo and associates,[58] who retrospectively analyzed 41 patients with appendiceal carcinoids accumulated at Massachusetts General Hospital in Boston between 1969 and 1990. Those authors reported that 80.5% of such tumors occurred in females. Moertel et al.[59] evaluated 150 patients with such lesions who were encountered at the Mayo Clinic over a period of 51 years and noted a male:female ratio of 0.4. In the late SEER subset, the overall age-adjusted incidence rate for white women was somewhat higher compared with white men (Table 11), and the overall crude male:female ratio was 0.82 (Table 10). This may reflect an increased number of pelvic procedures (such as laparoscopy) performed in women; thus, more incidental lesions, including carcinoids of the appendix, may be identified.

Appendiceal carcinoids tend to present at an early age (late SEER, 49.3 years, compared with 59.8 years for noncarcinoid tumors of the appendix). In the series reported by Roggo et al., the average age at diagnosis was 32 years.[58] It is interesting to note that in the Mayo Clinic series, patients who had tumors and metastases were younger (29 years) compared with patients who had smaller and clinically benign lesions (42 years).[59] In a separate series of 23 patients with appendiceal carcinoids occurring during childhood and adolescence, Moertel and colleagues[60] noted that although, in adults, these lesions most commonly are diagnosed as a result of incidental appendectomy, 78.3% of these younger patients presented with signs and symptoms of an acute abdomen. Moertel et al. also reported that the distribution of carcinoids within the appendix is not uniform, with the majority (67%) occurring at the tip of the structure rather than the base.

Although the female predominance and age distribution may reflect the primary indication for surgery, other possibilities may exist. In 1928, Masson[61] proposed that, unlike what occurs within other zones of the gastrointestinal tract, carcinoid tumors of the appendix originated from the subepithelial neuroendocrine cells. Shaw[62] evaluated the epithelial neuroendocrine cells (ENC) and subepithelial neuroendocrine cells (SNC) in 50 normal appendices and reported that, although the ENC were distributed equally within the appendix, the SNC were more numerous at the tip than at the base. Furthermore, although the density of ENC remained steady throughout life, SNC density was low in infants, but in a significant proportion of individuals, increased with age to a peak around the third decade, and thereafter slowly declined, returning to low levels in the elderly.

In the Mayo Clinic series, 4.7% of appendiceal carcinoid tumors metastasized, but no tumor measuring < 2 cm in greatest dimension exhibited metastatic spread.[59] Although, in the ERG group, the percentage of nonlocalized lesions was similar (5%) (Table 12), this value in the late SEER subset was significantly greater (39–45%). In the autopsy series by Berge and Linell, none of the patients with appendiceal carcinoids diagnosed at autopsy exhibited metastases.[25]

This observation also may reflect the fact that although the ERG registry recorded all appendiceal carcinoids until 1986, these lesions were reportable only to the SEER program if they were considered malignant. Despite the moderate percentage of associated noncarcinoid neoplasms (18.2%) associated with appendiceal carcinoids, the 5-year survival rate for patients with such lesions (71.0%) was among the best out of all types of carcinoids (Table 13). Numerous other reports confirm the favorable prognosis for patients with appendiceal carcinoids.[50,51,58–60] The reason for this relatively benign behavior may reflect either the specific cell type or the anatomic site of the lesion and its early or serendipitous detection. However, it is certain that the incidental, early discovery and simple management (i.e., appendectomy) of most appendiceal lesions contributes significantly to the excellent survival rate.

Colon

Carcinoid tumors of the nonappendiceal colon comprised 7.84% of the 13,715 tumors examined for this review. The most frequent site of colonic carcinoid was the cecum (34.5% of colonic carcinoids and 3.47% of all carcinoids within the late SEER subset) (Table 4). Ballantyne et al.[63] reported 54 patients with carcinoids of the colon who were identified by the Connecticut Tumor Registry between 1976 and 1986, 48% of which were located in the cecum. In their series, a slight female predominance (57%) and a marked white predominance (89%) were noted. It is possible that some cecal lesions actually arise from the base of the appendix and extend into the cecum; this process may help explain the reported preponderance of right-sided colonic carcinoids. Another possibility is the existence of a common cause for the apparent increased frequency of both carcinoids and adenocarcinoma in the right colon.[15] Similarly, in the late SEER registry, the population-corrected male:female ratio for colorectal carcinoids was 1.03 (Table 10), and the population-corrected black:white ratio was 1.73 (Table 7). However, noncarcinoid colorectal tumors exhibited predominance for whites (black:white ratio, 0.62) but demonstrated no notable gender bias (population-scaled male:female ratio, 1.06), possibly reflecting varying etiologic factors of specific tumor subtypes of the colon and rectum.

Extraappendiceal colonic carcinoids were nonlocalized in 55–67% of patients, a modest decline from the 71.0% nonlocalized classification in the ERG database (Table 12). Saha and associates reported a series of 13 patients with colonic carcinoid tumors in which 85% had metastatic disease at the time of diagnosis.[50] These patients exhibited the worst prognosis among all patients with carcinoid tumors of the gut (5-year survival, 41.6%). In the ERG group, the patients with carcinoids of the sigmoid colon exhibited the most unfavorable 5-year relative survival rates (33%).[10] Within the Connecticut Tumor Registry data, an overall 37% 5-year survival rate was noted; in the New Orleans series, the survival rate was 23%; for the Iowa registry, it was 20%.[50,51,63] The explanation for the more malignant biologic profile of colonic carcinoid tumors is not clear. In contrast, within the SEER registry, the overall 5-year relative survival rate for patients with adenocarcinoma of the colon was 60.4%.[12] Thomas and Sobin[15] have proposed that some colonic carcinoids previously were misdiagnosed and actually were poorly differentiated adenocarcinomas or undifferentiated carcinomas.

Rectum

Rectal carcinoids, overall, are the third most frequent group of the gastrointestinal carcinoid tumors (13.7% of 13,715 carcinoid tumors). It appears that the overall race, age, gender, and stage distribution for rectal carcinoids remained unaffected by the modified SEER case-reporting policy introduced in 1986. Jetmore et al.,[64] in their series of 170 patients with gastrointestinal carcinoids who were treated at the Ochsner Clinic between 1958 and 1990, reported that rectal carcinoids comprised 55% of all tumors. In other reports, the relative frequency of rectal carcinoids in relation to all carcinoid tumors varied between 5% and 27%, although many of those series were modest and highly selective and, thus, may not be completely representative.[46,50,51] Matsui and colleagues[65] reported 15 small rectal carcinoids (2–13 mm in greatest dimension) among 21,522 healthy individuals who underwent proctosigmoidoscopy in Toyama, Japan. Although other series noted male:female ratios of 1.7 and 2.8,[64,65] in the pan-SEER (1973–1999) data set, rectal carcinoids failed to exhibit any significant specific gender predominance (crude and corrected ratios of 1.07 and 1.13, respectively) (Table 10). The average age at diagnosis was 52 years and 48 years, respectively, in the studies by Jetmore et al.[64] and Matsui et al.;[65] in the late SEER group, the average age at diagnosis was 56.2 years. This is in contrast to an average age at diagnosis of 68.0 years for patients with noncarcinoid rectal tumors. Among the SEER data set, the age-adjusted incidence rates were approximately threefold greater in the gender-matched black population relative to white patients (Table 11). Rectal carcinoid tumors appear to exhibit a low propensity to metastasize and, thus, are associated with a favorable prognosis, as reflected by the small percentage of nonlocalized tumors (4–18%) (Table 12) and a high 5-year

survival rate (88.3%) (Table 13). A recent report suggests that there may be a number of different types of rectal carcinoids and that a generalization of this kind may not be valid for all patients.[66]

Nevertheless, these excellent outcome data also may reflect the expeditious diagnosis of such tumors, usually based on endoscopic rectal evaluation after the early presenting symptoms of hematochezia or pain. Mani et al.[9] evaluated more than 200 reports of rectal carcinoids and noted that tumor size and muscularis invasion were the two most important predictive criteria in the assessment of the malignant nature of these neoplasms. In analyzing data from the literature, those authors reported that at least 60% of carcinoids of the rectum diagnosed at biopsy measured < 1.0 cm in greatest dimension and that these lesions had metastasized in fewer than 2% of patients. In addition, metastatic spread in carcinoids measuring between 1.0 cm and 1.9 cm and in lesions measuring > 2 cm was evident in 10–15% and 60–80% of patients, respectively. Mani et al. concluded that rectal carcinoids measuring > 2 cm in greatest dimension or demonstrating evidence of muscularis invasion should be treated as though they were adenocarcinomas. Thus, the appropriate carcinoma-specific procedure should be performed, and the overall management of patients with hepatic or lymph node metastases should be no different than the treatment proposed for patients with other tumors of the rectum.[9]

Pancreas

Although no data regarding pancreatic carcinoids are available from the ERG and TNCS databases, the SEER registry has accrued 79 such patients since 1973. The parameters used to distinguish pancreatic carcinoids from islet cell neoplasia are not entirely clear; it is not readily apparent which criteria were applied to identify these lesions as carcinoids or whether attempts were made specifically to identify the peptide products of such lesions. Because many antibodies suitable for immunohistochemistry techniques have become available only recently, it is unlikely that such procedures were used in these cases. Nevertheless, carcinoids of the pancreas, although they are extremely rare (0.73% of all types of carcinoids within the pan-SEER data set) (Table 4), appear to constitute a particularly malignant form of carcinoid tumor. Thus, at the time of diagnosis, 72–81% of patients had nonlocalized disease, and the overall 5-year survival rate was only 37.5% (Tables 12,13). This is consistent with the usual pattern of late diagnosis and poor prognosis for almost all patients with pancreatic neoplasia, although it is ameliorated somewhat by the relatively indolent nature of carcinoid tumor biology compared with pancreatic adenocarcinoma. Thus, patients with pancreatic carcinoids may have the best outcome among all patients with pancreatic malignancies (SEER, 1973–1987: median survival > 12 months, with 84% of patients alive 1 year after diagnosis);[67] this compares favorably with the results from a retrospective meta-analysis of 119,000 patients with adenocarcinoma of the pancreas, in which Gudjonsson[68] noted an overall 5-year survival rate of merely 0.5%.

Respiratory Tract

Bronchial carcinoid tumors previously were termed *bronchial adenomas* because of their presumed benign nature. Such lesions, which previously were considered benign, were included within the SEER registry beginning in 1986. However, this aggregation of data appears not to have affected the overall age, gender, race, and stage distribution compared with previous data.[69] Davila et al.[70] reported that approximately 75% of bronchial carcinoids arise in the lobar bronchi, 10% occur in the mainstem bronchi, and 15% originate in the periphery of the lung. A somewhat different distribution pattern was noted by Blondal and associates,[71] who analyzed 46 patients with bronchopulmonary carcinoid tumors who were encountered between 1957 and 1976 in Uppsala, Sweden. In their series, 52% of the lesions were located in a main or lobar bronchus, with the rest found in the periphery of the lung. This suggests either a possible differential site-proclivity for carcinoids compared with adenocarcinomata of the lung or perhaps an unequal distribution of precursor cell types for each lesion. The absolute and relative frequency of bronchopulmonary carcinoids relative to all sites of carcinoid tumor has increased over time through all three series reported here (ERG, 10.2%; TNCS, 14.1%; pan-SEER, 27.9%) (Table 4). In the autopsy series by Berge and Linell and in the Swiss series of Levi et al., bronchopulmonary carcinoid tumors comprised 9% and 17.3% of all carcinoids, respectively.[25,30] In the ERG and late SEER databases, the crude male:female ratios recorded for these lesions were 0.8 and 0.51, respectively (Table 10); this female predominance was confirmed by other series (Levi et al. [Swiss canton series], 0.53; Uppsala series, 0.7).[30,71] Conversely, noncarcinoid tumors of the bronchopulmonary system exhibited a marked male predominance, although the extremely high male:female ratio noted in the ERG group (4.1) has declined in the past 20 years (late SEER, 1.36). Because smoking has long been implicated as a major etiologic factor in the genesis of lung carcinomas of certain histologic types, this decline may reflect alterations in the distribution of smokers and nonsmokers among

males and females. Moreover, this also suggests that carcinoid tumors and noncarcinoid tumors of the bronchopulmonary system have different etiologic factors.

The age-adjusted incidence rates for all races and both genders with bronchopulmonary carcinoids also have increased over the past 30 years (Table 11). This may reflect the changes in the designation of all such lesions as malignant and, thus, reportable to cancer registries. The average age at diagnosis of patients who have bronchopulmonary carcinoids is nearly a decade younger compared with patients who have noncarcinoid lung tumors (59.8 years vs. 68.5 years). Blondal et al.[71] noted that 76.1% of patients with bronchopulmonary lesions in their series presented with obvious symptomatology. The routine diagnostic use of fiberoptic bronchoscopy associated with the introduction of specific immunocytochemical techniques has further facilitated the early recognition and diagnosis of these lesions. In general, patients with bronchopulmonary carcinoids have a favorable prognosis. Overall, 27.5–34.6% of tumors were nonlocalized at diagnosis (Table 12) and the all-stage, 5-year survival rate was 73.5% (Table 13). This reflects a somewhat worse prognosis than was noted either in the Uppsala study (91% 5-year survival rate) or in a review of a number of other reported series (90%).[70,71] Soga and Yakuwa[72] recently described a series of 1875 tracheal and bronchopulmonary carcinoids within a Japanese carcinoid registry; significantly different 5-year postoperative survival rates were found between patients with typical and atypical carcinoid types (93.3% and 68.8%, respectively). Patients who had lung carcinoid tumors showed superior survival compared with patients who had other types of lung carcinoma.[73] Within the late SEER subset, other noncarcinoid tumors were associated with bronchopulmonary carcinoids in 23.4% of such patients.

Unusual and Rare Sites

It is important to recognize that carcinoid tumors may develop in virtually any organ of the abdomen or thorax. However, the small number of patients with esophageal tumors ($n = 6$ patients), hepatic tumors ($n = 45$), and gallbladder tumors ($n = 25$), and the lack of information regarding the diagnostic criteria used to identify them, make any specific conclusions difficult. Although sporadic reports have been published regarding renal and testicular carcinoids,[74–76] only three renal carcinoids and eight testicular carcinoids have been reported through the SEER registries (1973–1999). The prognosis of patients with carcinoid tumors in rare gastrointestinal sites remains poor (overall 5-year survival: liver, 18.4%; pancreas, 37.5%).

Synchronous or Metachronous Neoplasia

The coexistence of malignant tumors of different histologic types with carcinoids has been a source of significant debate throughout the past several decades. In the series by Berge and Linell, 40.7% of 199 patients with carcinoid tumors exhibited ≥ 1 coexisting second malignancies, one-third of which (35.8%) occurred in the gastrointestinal tract.[25] However, the authors also noted that malignant tumors were evident at approximately the same frequency (44.5%) in their autopsy series. However, because more recent clinical studies based on surgical specimens consistently have emphasized the apparently high frequency of second malignancies in patients with carcinoid tumors, the observations of Berge and Linell are coming into question. Their findings, however, may reflect the biology of the asymptomatic lesions identified at autopsy. Saha and colleagues[50] reported in their series of 112 patients with gastrointestinal carcinoids that a second malignancy was evident in 25% of patients. Of such lesions, 53% were adenocarcinoma of the gastrointestinal tract (colon, 25%; rectum, 14%; small bowel, 7%; stomach, 7%); the remainder occurred mostly in the lung (7%), prostate (7%), cervix uteri (7%), and other diverse sites. In a series of 55 patients with gastrointestinal carcinoid tumors presented by Marshall and Bodnarchuk,[46] secondary malignancies were noted in 18% of patients, 25% of which were colorectal carcinomas. Olney et al.[51] noted similar results in their assessment of 192 carcinoid tumors.

In the late SEER subset, carcinoid tumors in toto were associated with other noncarcinoid tumors in 22.4% of patients. An explanation for the high frequency of other neoplasia associated with carcinoid tumors remains unclear. It presumably reflects the fact that some of the bioactive agents secreted by these lesions are known mitogens for a variety of cell types. Therefore, it is probable that, over time, the prolonged action of such growth factors may promote phenotypic changes in susceptible cells and induce neoplastic transformation.[8,41] This may represent the *second hit* in cells of patients with a genetic predisposition to the development of carcinoid tumors. Analysis of the current data and other reports suggests that if a carcinoid tumor is identified, particularly in the small intestine, appendix, or colon, then it is appropriate and prudent to undertake surveillance on a regular basis of the colon, rectum, small intestine, lung, and (in female patients) the cervix and ovaries.

Multiple Carcinoids

In the SEER registry of 10,878 patients with at least 1 carcinoid tumor, 125 patients (1.15%) with > 1 carci-

noid tumor were identified, with a mean of 2.5 distinct tumor-laden sites. Early SEER and late SEER subgroup analyses reveal multiple carcinoid rates of 0.80% and 1.56%, respectively; the average number of involved sites remained stable (2.47–2.43) between those two periods. The existence of such tumors, in part, may hold the key to the unique pathobiology of carcinoid tumors, because multicentricity suggests either exposure to a common luminal pathogen or a regional clonal abnormality. Berge and Linell reported in the Malmo autopsy series[25] that multiple carcinoids were evident in 50 of 152 patients (33%) with small intestinal carcinoids; in 2 patients, carcinoids were found at 2 different sites (appendix–ileum and ileum–colon). Watson et al.[76] noted that in 318 patients with carcinoid tumors, 7 multiple small intestinal carcinoids (5 in the ileum and 2 in the jejunum) were identified at surgery (12.3% of all small intestinal lesions). In that series, the number of tumors at 1 site ranged from 3 to 10 tumors. In a series by Saha and colleagues,[50] 10% of the patients had tumors at multiple sites, and 82% were located in the small bowel. The propensity of small bowel carcinoids to develop as multiple lesions is not understood well. One possible explanation is that the malignant transformation of the specific stem cells from which these tumors originate may be driven by an exogenous growth factor that is capable of influencing similar cells in disparate locations. The validity of this hypothesis is exemplified best by the multiple fundic gastric carcinoids that occur in response to hypergastrinemia associated with chronic atrophic gastritis or gastrinomas associated with the MEN-1 syndrome.[73]

Metastases

In the Malmo autopsy series compiled by Berge and Linell,[25] metastases were identified in 29.4% of patients; the majority of metastases (61.2%) originated from the small intestine. Overall, in addition to the lymph nodes (89.8%), the most frequent sites of metastatic carcinoids were the liver (44.1%), lung (13.6%), peritoneum (13.6%), and pancreas (6.8%). The liver also has been noted by other authors as the most frequent site for carcinoid metastases.[50,76] Olney et al.[51] reported in their series that ileal lesions (40%), cecal lesions (66.7%), and colonic lesions (44.4%) metastasized most frequently. Marshall and Bodnarchuk[46] noted in their series that metastatic disease was evident in 68% of 19 ileal carcinoids and in 100% of 5 cecal carcinoids. Similarly, in the late SEER subgroup, the highest percentage of nonlocalized lesions was noted for esophageal, small intestinal, cecal, and pancreatic carcinoids (66.7%, 58.3–64.1%, 81.5–83.2%, and 71.9–81.3%, respectively), compared with the overall percentage of nonlocalized lesions for all carcinoids (32.1–46.7%) (Table 12). To explain the high metastatic potential of small intestinal and colonic carcinoids, further information regarding the pathobiology of these tumors is needed.

CONCLUSIONS

This review of 13,715 patients with carcinoid tumors spans nearly 50 years and represents the largest known and longest such aggregation. In addition, the data pool is such that, overall, it may be regarded as a fair sample of the United States population as a whole. Critical examination of the data and time distribution of these patients reveals several important findings and trends that will aid the further examination of this disease and provide additional epidemiologic insight. The incidence of carcinoid has increased over the past 5 decades; this may be secondary to true in vivo changes or to improvements in disease detection. The percentage of carcinoid tumors among all tumors occurring at specific sites has increased for the stomach and rectum but has decreased for the appendix. Certain carcinoid tumors, such as those of the rectum, are exceedingly prevalent among black and Asian populations within the United States, whereas persons of Hispanic descent are diagnosed with carcinoid tumor at a lower rate than might be expected, suggesting that genetic factors may play a role in the differential development of this disease.

Although, over the past 30 years, the study of neuroendocrine tumors has been advanced significantly by the elucidation of aspects of carcinoid biology and the development of novel diagnostic methodology, there appears to be little change in terms of outcome. Despite the use of specific antibodies in immunohistochemistry to identify neuroendocrine tumors and more precise identification of lesions that previously were not clearly evident as neuroendocrine in origin, there remains confusion regarding the classification of carcinoid tumors. Of positive clinical relevance has been the widespread utilization of endoscopy, ultrasonography, computerized axial tomography, and somatostatin scintigraphy, all of which have enhanced significantly the identification of previously undetectable lesions and, hence, have allowed more accurate delineation of metastases. Thus, some of the changes appreciated in the epidemiology of carcinoid tumors may reflect improvements in technology.

The somewhat underwhelming change in survival apparent in the analysis of the data of the last 50 years indicates that the failure to identify the precise biology of these lesions still confounds the development of adequate therapeutic strategies. In general, it appears

that current optimal therapeutic strategy for carcinoid tumors should be based on the appreciation of the obviously malignant yet somewhat restrained biologic behavior of these lesions. Thus, overly radical management does not appear justified, although a diligent search for associated noncarcinoid tumors appears prudent and relevant. The assessment of the current database confirms that the future of the elucidation of this disease process requires correlation with precise cellular and biologic determinants of malignancy as well as a delineation of the specific cell of origin and its precise genomic configuration. The availability of such data will facilitate predictions of the rate of tumor growth and the likelihood of metastatic dissemination, thus allowing optimization of therapeutic intervention. Further rigorous evaluation of the epidemiology of carcinoid disease may provide basic insights into the etiopathology of these fascinating but poorly understood lesions. Indeed, as this study demonstrates, the broad hinterland of the disease is apparent; however, the precise topography, both biologic and genomic, remains for the most part uncharted.

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