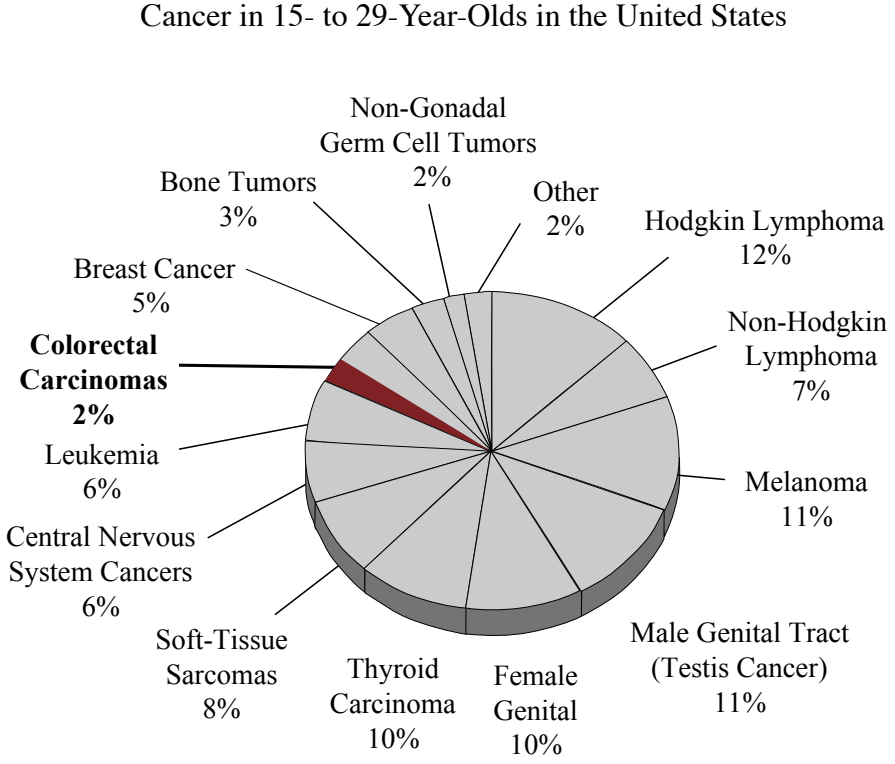
Chapter 10

Colon and Rectal Cancer



Sheri Spunt, MD

Wayne Furman, MD

Michael La Quaglia, MD

Melissa Bondy, PhD

Richard Goldberg, MD

HIGHLIGHTS

Incidence

- Colorectal carcinoma occcurs in adolescents and young adults at an incidence that increases exponentially between 10 and 35 years of age.
- During 1975 to 2000, colorectal cancer accounted for 2.1% of all neoplasms diagnosed in 15- to 29-year-olds.
- In the year 2000, an estimated 432 individuals 15 to 29 years of age were diagnosed with cancer of the colon.
- The incidence of colorectal carcinoma relative to other cancers rose from 1% in the 15- to 19-year age group, to 1.7% in the 20- to 24-year age group, to 2.7% in the 25- to 29-year age group.
- Males had a higher incidence of colorectal carcinoma than females at all ages, except in individuals 15 to 19 years of age.
- Although the incidence of colorectal carcinoma in individuals over 45 years declined during the period 1975 to 2000, the incidence in 15- to 29-year-olds increased.
- The incidence of colorectal carcinoma was approximately equal in white non-Hispanics, Hispanics, African Americans/blacks, and Asians/Pacific Islanders who were 15 to 29 years of age when diagnosed.
- American Indians/Alaska Natives between 20 and 35 years of age tended to have a lower incidence of colorectal carcinoma than other racial/ethnic groups.

Mortality & Survival

- Five-year survival for individuals 15 to 29 years of age was similar to that of older individuals.
- Colorectal carcinoma survival improved over time, although it remained relatively stable for individuals in the 15- to 29-year age group.
- A 54% 5-year survival rate for colorectal carcinoma for the age group was achieved in the era 1975 to 1980; the 5-year survival rate increased to 58% in the era 1993 to 1999.
- Females had higher 5-year survival rates than males at virtually all ages; the disparity was particularly marked in individuals 15 to 29 years of age.
- African Americans/blacks in the 15- to 29-year age group had the worst survival, approximately 20% worse than whites, non-Hispanics, and Asians/Pacific Islanders.
- Whites tended to have the best prognosis.

Risk Factors

- Predisposing factors for colorectal carcinoma in children and young adults include hereditary conditions (polyposis and non-polyposis syndromes), inflammatory bowel disease, and prior radiation exposure.
- Hamartomatous polyposis syndromes carry a lower risk of colorectal carcinoma than adenomatous polyposis syndromes.

INTRODUCTION

Although colorectal carcinoma is among the most common malignancies of adulthood, the disease is uncommon in adolescents and young adults. Between 1975 and 2000 in the U.S., colorectal carcinoma accounted for 2.1% of all neoplasms in adolescents and young adults 15 to 29 years of age. In the year 2000, 432 individuals in this age group were diagnosed with colorectal carcinoma in the U.S.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

The International Classification of Childhood Cancer (ICCC) has no specific category for colorectal cancer. These cancers are contained with category XI(f), *Other and Unspecified Carcinomas*, as one of the *Carcinomas and Other Epithelial Neoplasms* (category XI). Hence, the SEER site recode based on the International Classification of Diseases for Oncology (ICD-O) was used exclusively for this chapter.

Table 10.1: *Incidence of Colorectal Carcinoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	^	^	0.6	2.0	5.6	14.6
Average annual % change in incidence, 1975-2000, SEER	^	^	0	0	0	0
Estimated incidence per million, year 2000, U.S.	^	^	0.6	2.0	5.6	14.6
Estimated number of persons diagnosed, year 2000, U.S.	^	^	13	41	107	284

^ Too few for a reliable estimate

For colorectal cancer, the ICD-O Topographical categories are C18.0-C20.9, C26.0 (colon, rectum, and intestine NOS) and the ICD-O Morphologic categories include general carcinomas and adenocarcinomas (8010-8041, 8140, many others) and specific cancers of the colon/rectum. The latter include carcinoid tumors (8240-8245). No attempt was made to separate cancer of the colon from rectal cancer. Cancer of the anus is not included in this chapter.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

Since the ICCC was set up as a classification for childhood cancer, it does not have a separate category for colorectal cancer. Topography and histology from ICD-O can be used to examine differences among very young colorectal cancer patients compared to older patients, but it is clear that this method needs to be complemented with other biologic determinants such as microsatellite instability, which is far more common in the colorectal carcinomas that occur in adolescents and young adults, as opposed to the sequential gene mutations—including p53 mutations—that occur in older adults.

INCIDENCE

According to SEER data, colorectal carcinoma accounted for 2.1% of all malignancies diagnosed in individuals 15 to 29 years of age between 1975 and 2000, and occurred at a rate of 7.21 per million, age adjusted to the 2000 census and to 5-year age intervals. It was the 11th most common cancer in this age bracket. By using the data in *Trends in Incidence* (section below), a total of 432 new cases of colorectal cancer were estimated to have been diagnosed in the U.S. in the year 2000 (Table 10.1).

Age-Specific Incidence

The striking dependence of the incidence of colorectal carcinoma on age is shown in Figure 10.1. During 1975 to 2000, it increased exponentially between ages 10 and 35, as highlighted by the red line in the semilog plot in the inset to figure 10.1.

Figure 10.2 shows the incidence of colorectal carcinoma relative to that of all cancers in 5-year age groups from 0 to 44 years. The incidence of colorectal carcinoma relative to all cancers increased steadily with advancing age—again, even within the 15- to 29-year age group.

Gender-Specific Incidence

The incidence of colorectal carcinoma in males and females was similar before age 20, and higher in males than females older than 20 years. The predilection for male gender increases with age, such that by 50 years of age, males had a nearly 50% greater incidence (Figure 10.3).

Racial/Ethnic Differences in Incidence

The incidence of colorectal carcinoma was approximately equal in white non-Hispanics, Hispanics, African Americans/blacks, and Asians/Pacific Islanders who were 15 to 29 years of age when diagnosed (Figures 10.4 and 10.5 [the log version of 10.4]). American Indians/Alaska Natives between 20 and 35 years of age tended to have a lower incidence of colorectal carcinoma than other racial/ethnic groups. African Americans/blacks had a lower incidence from 0 to 20 years of age (Figure 10.5).

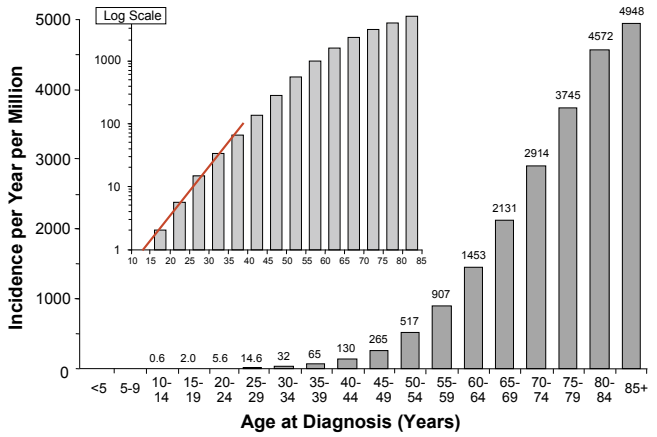


Figure 10.1: Incidence of Colorectal Carcinoma, SEER 1975-2000

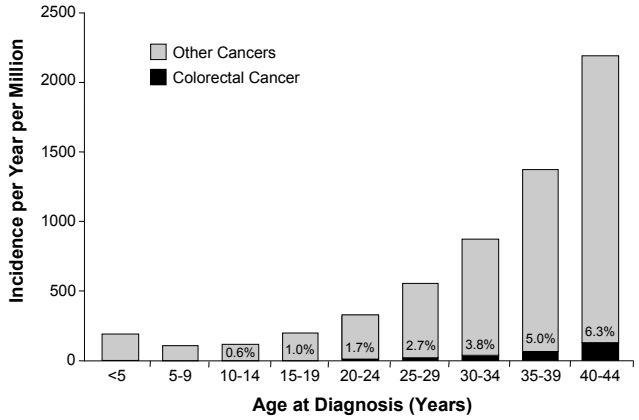


Figure 10.2: Incidence of Colorectal Cancer Relative to All Cancer, SEER, 1975-2000

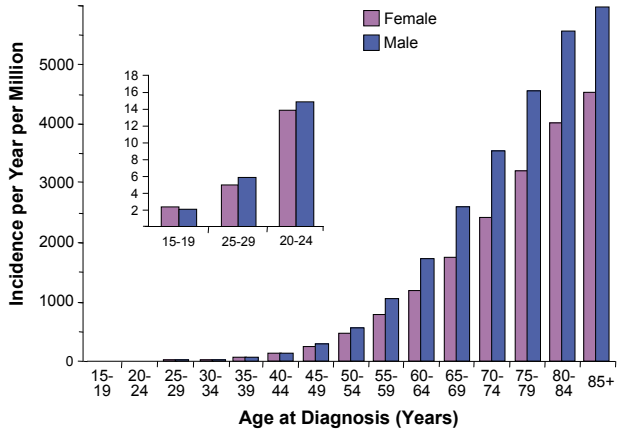


Figure 10.3: Incidence of Colorectal Carcinoma by Gender, SEER 1975-2000

Trends in Incidence

Figure 10.6 displays the incidence of colorectal carcinoma in 5-year age groups over 4 time periods: 1975 to 1980, 1981 to 1986, 1987 to 1992, and 1993 to 2000. For individuals over 45 years of age, the incidence in the most recent time period (1993 to 2000) was lower than during earlier years.

As shown in Figure 10.7, a decline in colorectal carcinoma incidence in younger individuals was not readily apparent. The rarity of colorectal carcinoma in patients under 45 years of age may explain the difficulty in identifying a trend in incidence in this age group.

Figure 10.8 displays the average annual percent change in incidence of colorectal carcinoma by age group during the years 1975 to 2000. The incidence of colorectal carcinoma in patients in the 15- to 29-year age group increased during this period, whereas the incidence in patients over 30 years of age declined.

OUTCOME

Mortality

As with incidence (Figure 10.7), mortality of colorectal cancer was directly proportional to age and was higher in males than females (Figure 10.9). In the U.S., African Americans/blacks had higher mortality from colorectal carcinoma than any other racial/ethnic group. This was true not only for older adults but also for young adults 25 years of age and older (Figure 10.10).

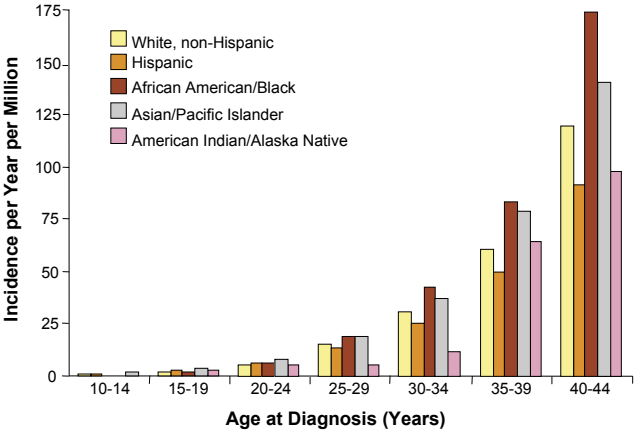


Figure 10.4: Incidence of Colorectal Carcinoma by Race/Ethnicity, SEER 1992-2000

Since 1975, colorectal carcinoma mortality has declined among 15- to 29-year-olds (Figure 10.11), despite the increased incidence in this age group (Figure 10.8). The reduction in national colorectal cancer mortality during the past quarter century averaged 1.4% per year in patients younger than age 45 ($p < 0.05$), and the decline was also statistically significant in each 5-year age group under age 45 (Figure 10.12). There is a suggestion that the trend in national colorectal cancer mortality reduction is directly proportional to age, with patients younger than 35 years of age experiencing less of a reduction in mortality than those 35 to 44 years of age (Figure 10.12).

Survival

Five-year survival of individuals with colorectal carcinoma 15 years of age and older was between 50% and 61% for all five-year age groups (Figure 10.13). Five-year survival rates improved in successive eras, though rates for individuals 15 to 29 years of age remained relatively stable (Figure 10.14).

Gender-Specific Survival

Females had a consistently higher 5-year survival rate compared to males; this was most apparent in patients younger than 40 years of age (Figures 10.15 and 10.16)

Racial/Ethnic Differences in Survival

Survival—as a function of race/ethnicity—for 15- to 29-year-olds diagnosed with colorectal cancer during the period 1992 to 1999 is shown in Figure 10.17. African Americans/blacks had the worst survival in this age group. White non-Hispanics, Hispanics, and

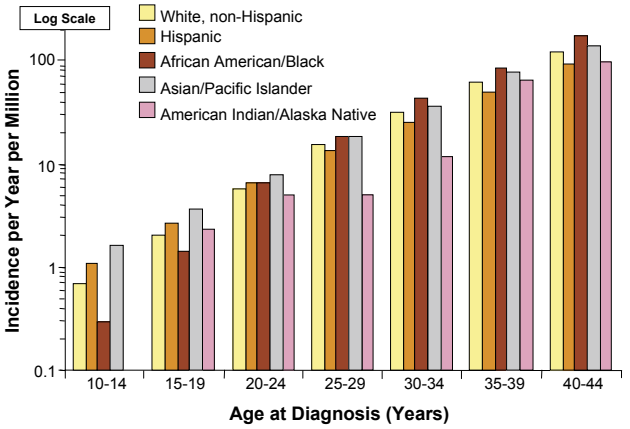


Figure 10.5: Incidence of Colorectal Carcinoma by Race/Ethnicity, SEER 1992-2000

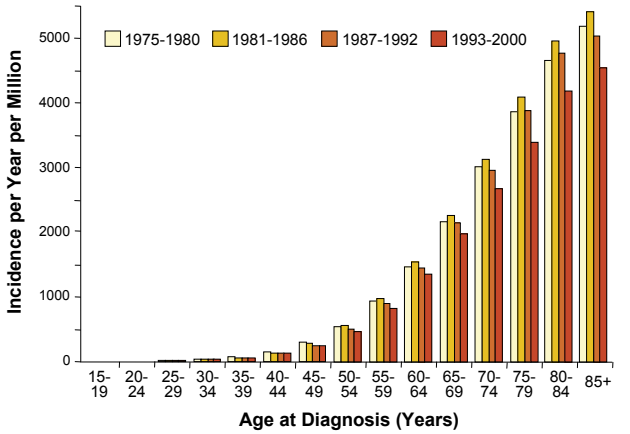


Figure 10.6: Change in Incidence of Colorectal Carcinoma by Era, SEER 1975-2000

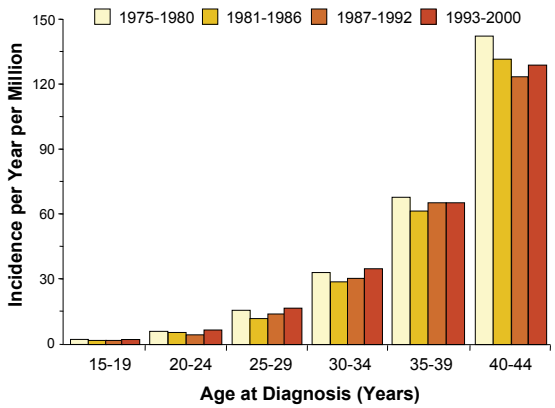


Figure 10.7: Change in Incidence of Colorectal Carcinoma by Era, SEER 1975-2000

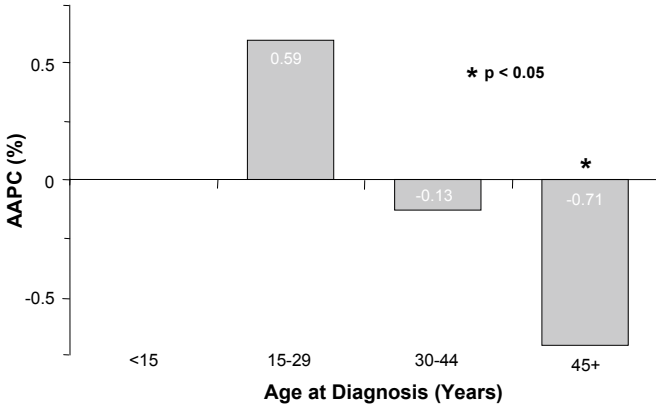


Figure 10.8: Average Annual Percent Change (AAPC) in Incidence of Colorectal Carcinoma, SEER 1975-2000

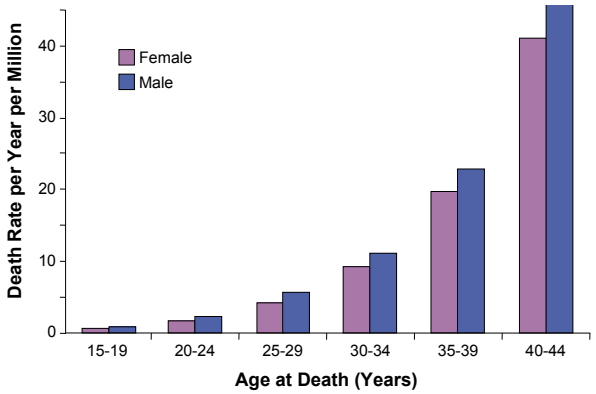


Figure 10.9: National Mortality of Colorectal Carcinoma by Gender, U.S., 1975-2000

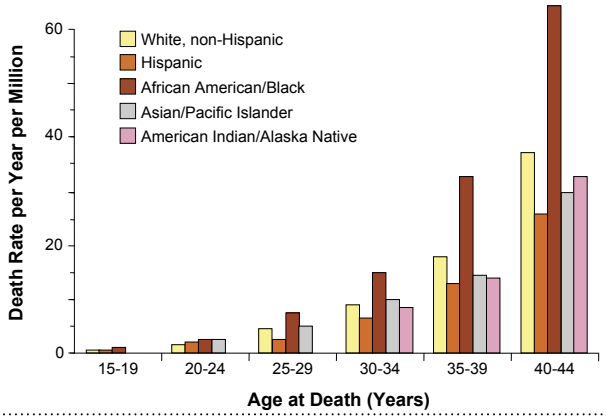


Figure 10.10: National Mortality of Colorectal Carcinoma by Race/Ethnicity, U.S., 1975-2000

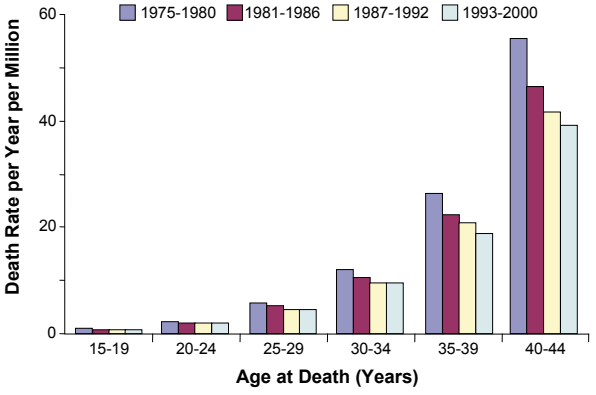


Figure 10.11: National Mortality of Colorectal Carcinoma by Era, U.S

Asians/Pacific Islanders had comparable survival, which was from 15% to 20% better than for African Americans/blacks as early as 1 year after diagnosis and persisting for at least five years. Whites (including Hispanic whites) tended to have the best prognosis.

Survival According Extent of Disease

Figure 10.18 displays 5-year survival rates for individuals with colorectal carcinoma according to disease extent. There were no apparent differences in survival in individuals 15 to 29 years of age compared to older individuals.

RISK FACTORS

Predisposing factors for colorectal carcinoma in children and young adults include hereditary conditions affecting the bowel (polyposis and nonpolyposis syndromes), inflammatory bowel disease, and radiation exposure. Approximately 15 to 20% of colorectal cancer patients have familial colon cancer without a defined genetic pattern,[1] about 5% have hereditary nonpolyposis colon cancer,[2] and 1% have hereditary polyposis syndromes.[3]

Hereditary Nonpolyposis Colon Cancer (HNPCC)

HNPCC was defined by Lynch,[4] who observed a number of families with an increased risk of colon cancer in the absence of polyposis. HNPCC accounts for approximately 5% of all colorectal cancer cases and is associated with an early age at diagnosis, proximal colonic site predominance, mucinous phenotype and multiple synchronous and metachronous tumors.[5,6] Families with HNPCC also have a higher incidence of other tumors, including stomach, small intestine, hepatobiliary system, ovary,

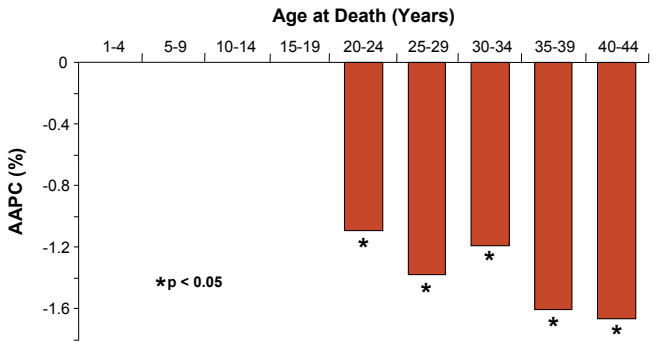


Figure 10.12: Average Annual Percent Change (AAPC) in National Mortality, Colorectal Carcinoma, 1975-2000

endometrium, and upper urinary tract cancers.[7] HNPCC is associated with a lower stage at diagnosis, a lower incidence of metastases, and a better prognosis than sporadic colorectal carcinoma.[8]

Germline mutations of DNA mismatch repair genes are responsible for the predisposition to colorectal carcinoma among patients with HNPCC. Absence of normal mismatch repair function in colonic epithelial cells leads to microsatellite instability and malignant transformation.[9] The Amsterdam criteria for defining HNPCC[10] include colorectal cancer in at least three individuals spanning two generations, at least one of whom is a first-degree relative of the other two. In a small series of colorectal cancer patients who were 21 years of age or less at diagnosis, microsatellite instability was observed in about half, though few fulfilled the diagnostic criteria for HNPCC.[11]

Polypoid Disease of the Gastrointestinal Tract

Colonic polyps can be divided by histology into adenomatous and hamartomatous categories. Adenomatous polyps represent a growth alteration in the colonic mucosa resulting in neoplastic proliferation and substantial malignant potential. Hamartomatous polyps, though less proliferative in nature, are also associated with a significant cancer risk.

Hamartomatous Polyposis Syndromes

Only two hamartomatous polyposis syndromes have been clearly associated with an increased risk of colorectal carcinoma. Juvenile polyposis, which encompasses juvenile polyposis coli and diffuse juvenile polyposis,

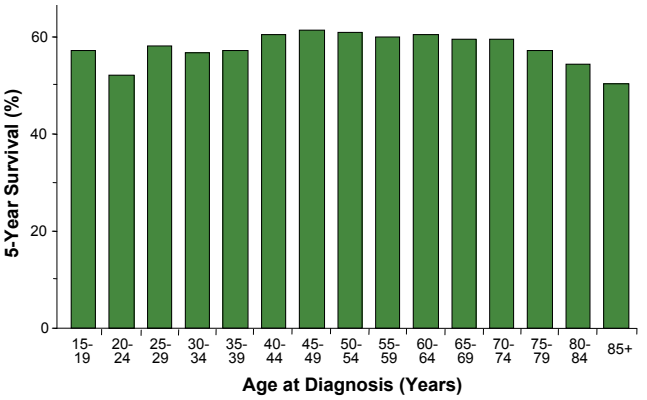


Figure 10.13: 5-Year Survival Rate for Colorectal Carcinoma, SEER 1975-1999

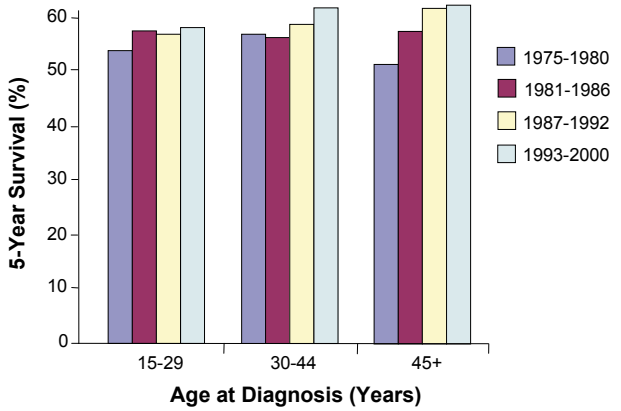


Figure 10.14: 5-Year Survival Rate for Colorectal Carcinoma by Era, SEER

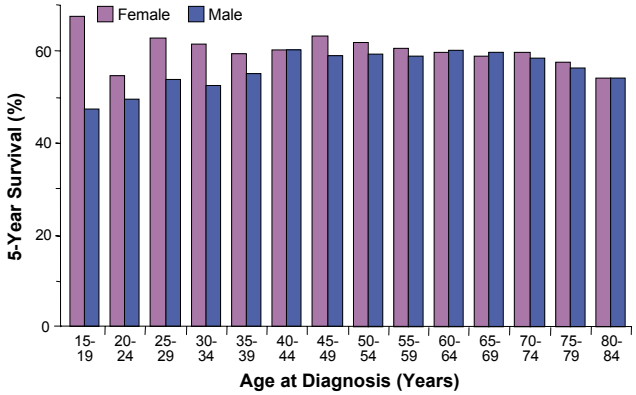


Figure 10.15: 5-Year Survival Rate for Colorectal Carcinoma by Gender, SEER 1975-1999

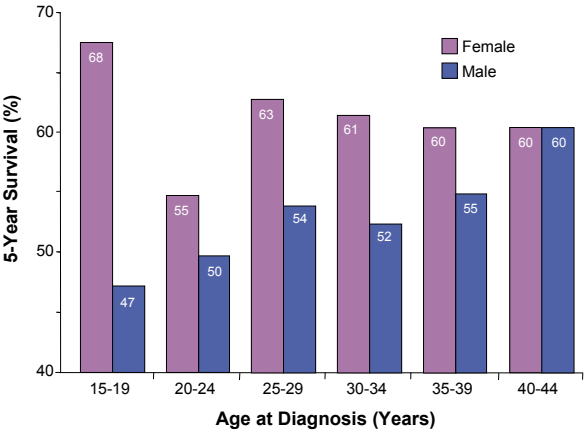


Figure 10.16: 5-Year Survival Rate for Colorectal Carcinoma by Gender, SEER 1975-1999

typically presents with rectal bleeding and anemia in patients between 4 and 30 years of age.[12,13] Other symptoms include intussusception or bowel obstruction, rectal or polyp prolapse, abdominal pain, and protein-losing enteropathy. The polyps may occur throughout the gastrointestinal tract, but most often affect the stomach, distal colon, and rectum. Juvenile polyposis is transmitted as an autosomal dominant trait; SMAD4 and BMPR1A gene mutations have been implicated in the etiology of this syndrome.[14] In a review of cases reported in the English literature, Coburn et al. found that 17% of patients developed gastrointestinal malignancies, at a mean age of 35.5 years (range, 4-60 years).[15] The cumulative risk of colorectal malignancy has been reported to be 68% by 60 years of age.[16]

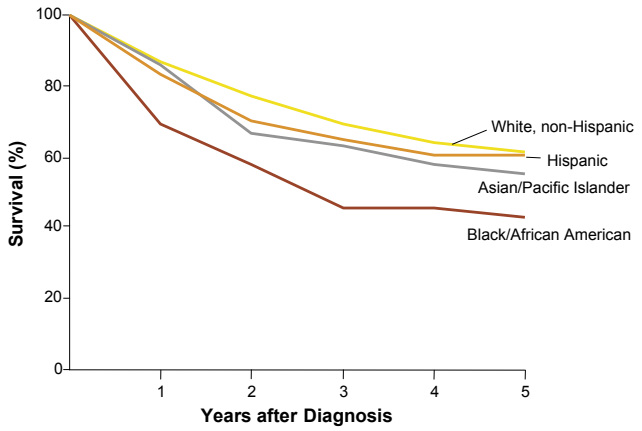


Figure 10.17: Relative Survival for Colorectal Carcinoma by Race/Ethnicity, SEER 1992-1999

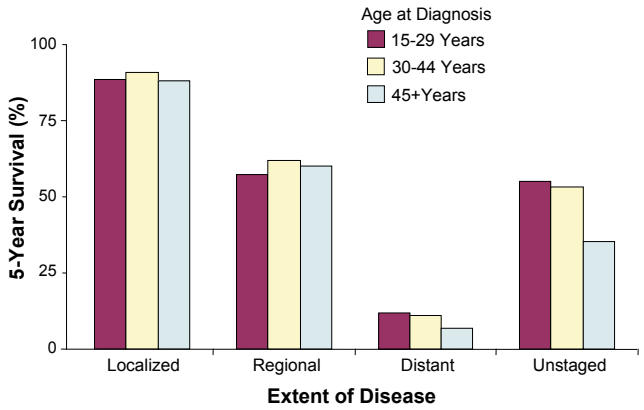


Figure 10.18: 5-Year Survival Rate for Colorectal Cancer by Extent of Disease, SEER 1975-2000

Peutz-Jeghers syndrome,[17] characterized by variable mucocutaneous pigmentation abnormalities and gastrointestinal hamartomas, is also associated with an increased risk of colorectal malignancy. These patients typically present during childhood with recurrent intussusception/bowel obstruction, rectal bleeding, anemia, and rectal prolapse, in some cases before the pigmentary changes classically associated with the disorder are present.[18] Males become symptomatic at an earlier age (peak 5-10 years) than females (peak 10-15 years). Hamartomatous polyps of the small intestine are most common; however, about one-third of patients also have colorectal involvement. Most cases of Peutz-Jeghers syndrome are due to germline mutation of the STK11 gene, which encodes a serine threonine kinase.[19] The transformation from hamartoma to adenocarcinoma in patients with germline STK11 mutations depends on additional somatic mutations.[20] In an analysis of 33 patients with Peutz-Jeghers syndrome, the standardized mortality ratio for gastrointestinal cancer was 24.8.[21]

Adenomatous Polyposis Syndromes

The familial adenomatous polyposis (FAP) syndromes are characterized by the early development of multiple adenomatous colonic polyps. FAP affects about 1 in 7,000 individuals.[9] Virtually all patients with FAP will develop colorectal carcinoma unless a total colectomy is performed prior to the onset of malignancy. FAP is an autosomal dominant trait with high but variable penetrance; 10 to 20% of cases are *de novo* mutations without any apparent family history. Mutations in the APC gene at 5q21 are responsible for the FAP syndrome.[22] The clinical phenotype, including the presence or absence of extracolonic abnormalities, appears to vary according to the exact site of APC gene mutation and the presence of modifying genes.[23,24] Two types of FAP seem to exist, and a relationship between the location of mutations in the gene and the phenotypic expression of FAP has been established:[25] the sparse type, which is characterized by hundreds of polyps, and the profuse type, which presents with thousands of polyps. Patients with the profuse type tend to develop adenocarcinoma at an earlier age. FAP is associated with the development of extracolonic malignancies, including periampullary and thyroid carcinomas and hepatoblastoma.[26,27]

A proportion of FAP patients have Gardner's syndrome,[28] which includes desmoid tumors, cysts of the mandible, fibromas, osteomas, and congenital hypertrophy of the retinal pigment epithelium. Desmoid tumors of the abdominal wall and mesentery occur in a significant proportion of these patients, and are a leading cause of death in post-colectomy patients.

Other syndromes associated with FAP include Turcot's syndrome[29] and Oldfield's syndrome.[30] Patients with Turcot's syndrome manifest multiple pediatric brain tumors (medulloblastoma, gliomas, and others) in conjunction with FAP. Hamilton et al. found that two distinct germline defects, mutation of the APC gene and mutation of a mismatch-repair gene may each give rise to Turcot's syndrome.[31] The type of brain tumor correlates with the mutation, with medulloblastomas characteristic of APC-related mutations and glioblastoma multiforme seen in patients with mismatch-repair gene mutations. Oldfield's syndrome includes FAP in association with multiple sebaceous cysts.

Inflammatory Bowel Disease

Ulcerative colitis is clearly associated with the development of colorectal carcinoma.[32] The age at initial presentation and extent of colonic involvement are strong independent risk factors for subsequent development of colorectal cancer.[33] Patients less than 15 years of age at diagnosis and those with involvement of the entire colon are at the highest risk. The cumulative risk of colorectal carcinoma in individuals less than 40 years of age with pancolitis was 13% at 25 years from diagnosis. Synchronous colorectal tumors are more common in patients with ulcerative colitis than in the remainder of the population with colorectal carcinoma.[34] In a report by Lashner et al.,[35] 11 of 15 ulcerative colitis patients with strictures were found to have carcinomas on biopsy. Thus, patients who develop colonic strictures should be considered to have carcinomas until proven otherwise, and stricture formation is an indication for surgery.

Crohn's disease, when it involves the colon or rectum, is associated with an increased risk of colorectal carcinoma. The relative risk is quite high (20.9 odds ratio) in those in whom the diagnosis is made before the age of 30 years.[36] About one-third of the colorectal carcinomas in patients with Crohn's disease are mucinous adenocarcinoma.[37]

Other Factors Predisposing to Colorectal Carcinoma

Colorectal carcinoma has been reported in patients with Bloom syndrome, a rare autosomal recessive disorder caused by germline mutations of the BLM gene.[38] Gruber et al. showed recently that carriers of BLM mutations are also at increased risk of colorectal carcinoma.[39] About 5% of patients undergoing urinary diversion with ureterosigmoidostomy develop colon cancer, probably due to chronic inflammation caused by the mixture of feces and urine at the implant site.[40]

Colorectal Carcinoma in Childhood Cancer Survivors

Children who receive abdominal or pelvic radiation therapy for the treatment of a malignancy are at increased risk for early development of colorectal cancer in the radiation field.[41,42] This may be particularly problematic in any child who has one of the above genetic predispositions. Overall, however, colorectal cancer is one of the least common second cancers in long-term survivors of childhood cancer.[43-46]

SUMMARY

Colorectal carcinoma accounted for 2.1% of all malignancies in individuals between 15 and 29 years of age, and was the 11th leading cause of cancer in this age group. The average annual incidence of colorectal carcinoma was 7.2 per million in 15- to 29-year-old individuals. The incidence of colorectal carcinoma rose with advancing age, even within the 15- to 29-year age group. Colorectal carcinoma accounted for an increasing proportion of all malignancies with advancing age. While it accounted for only 1% of malignancies in the 15- to 19-year age group, it was responsible for 2.7% of cancers in the 25- to 29-year age group. Colorectal carcinoma was more common in males at all ages over 20 years of age. Although the incidence of colorectal carcinoma has declined over time in individuals over 45 years of age, a similar decline has not been observed in individuals in the 15- to 29-year age group. The small number of patients diagnosed with colorectal carcinoma in this age group makes it difficult to draw conclusions about incidence and outcome data. The average percent annual change in the incidence of colorectal carcinoma increased between 1975 and 2000 among individuals 15 to 29 years of age, and declined in individuals over 30 years of age.

Five-year survival rates for individuals with colorectal carcinoma in the 15- to 29-year age group were similar to those for older individuals. The survival improvements over time observed in individuals over 45 years of age have also been noted in individuals 15 to 29 years of age. Females with colorectal carcinoma had a superior 5-year survival compared to males at virtually all ages; the disparity was particularly marked in individuals younger than 40 years of age.

Risk factors for the development of colorectal carcinoma in childhood and young adulthood include hereditary conditions (polyposis and non-polyposis syndromes), inflammatory bowel disease, and radiation exposure. Hamartomatous polyposis syndromes carry a lower risk of colorectal carcinoma than adenomatous polyposis syndromes. Colorectal carcinoma has also been reported in individuals with Bloom syndrome and in those who have undergone urinary diversion via ureterosigmoidostomy.

REFERENCES

1. Boutron M-C, Faivre J, Quipourt V, et al.: Family history of colorectal tumours and implications for the adenoma-carcinoma sequence: a case control study. Gut 1995;37:830-4.
2. Marra G, Boland CR: Hereditary nonpolyposis colorectal cancer: the syndrome, the genes, and historical perspectives. J Natl Cancer Inst 1995;87:1114-25.
3. Vogelstein B: Genetic testings for cancer: the surgeon's critical role. Familial colon cancer. J Am Coll Surg 1999;188:74-9.
4. Lynch HT, de la Chapelle A: Genetic susceptibility to non-polyposis colorectal cancer. J Med Genet 1999;36:801-18.
5. Lynch HT, Smyrk T, Lynch J: An update of HNPCC (Lynch syndrome). Cancer Genet Cytogenet 1997;93:84-99.
6. Mecklin JP, Sipponen P, Jarvinen H: Histopathology of colorectal carcinomas and adenomas in cancer family syndrome. Dis Colon Rectum 1986;29:849-53.
7. Watson P, Lynch HT: Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993;71:677-85.
8. Watson P, Lin KM, Rodriguez-Bigas MA et al.: Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. Cancer 1998;83:259-66.
9. Kinzler KW, Vogelstein B: Lessons from hereditary colorectal cancer. Cell 1996;87:159-70.
10. Vasen HF, Mecklin JP, Meera Khan P, et al.: The International Collaborative Group on Herediatry Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991;34:424-5.
11. Datta RV, LaQuaglia MP, Paty PB: Genetic and phenotypic correlates of colorectal cancer in young patients. N Engl J Med 2000;342:137-8.
12. Luk GD: Diagnosis and therapy of hereditary polyposis syndromes. Gastroenterologist 1995;3:153-67.
13. Desai DC, Neale KF, Talbot IC, et al.: Juvenile polyposis. Br J Surg 1995;82:14-7.
14. Sayed MG, Ahmed AF, Ringold JR, et al.: Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. Ann Surg Oncol 2002;9:901-6.
15. Coburn MC, Pricolo VE, DeLuca FG, et al.: Malignant potential in intestinal juvenile polyposis syndromes. Ann Surg Oncol 1995;2:386-91.
16. Murday V, Slack J: Inherited disorders associated with colorectal cancer. Cancer Surv 1989;8:139-57.
17. Jeghers H, McKusick VA, Katz KH: Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. N Engl J Med 1949;241:1031-6.
18. Tovar JA, Eizaguirre I, Albert A, et al.: Peutz-Jeghers syndrome in children: report of two cases and review of the literature. J Pediatr Surg 1983;18:1-6.
19. Jenne DE, Reimann H, Nezu J, et al.: Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 1998;18:38-43.
20. Gruber SB, Entius MM, Petersen GM, et al.: Pathogenesis of adenocarcinoma in Peutz-Jeghers syndrome. Cancer Res 1998;58:5267-70.

21. Lim W, Hearle N, Shah B, et al.: Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome. Br J Cancer 2003;89:308-13.
22. Kinzler KW, Nilbert MC, Su LK, et al.: Identification of FAP locus genes from chromosome 5q21. Science 1991;253:661-5.
23. Caspari R, Olschwang S, Friedl W, et al.: Familial adenomatous polyposis: desmoid tumours and lack of ophthalmic lesions (CHRPE) associated with APC mutations beyond codon 1444. Hum Mol Genet 1995;4:337-40.
24. Scott RJ, Taeschner W, Heinimann K, et al.: Association of extracolonic manifestations of familial adenomatous polyposis with acetylation phenotype in a large FAP kindred. Eur J Hum Genet 1997;5:43-9.
25. Spirio L, Otterud B, Stauffer D, et al.: Linkage of a variant or attenuated form of adenomatous polyposis coli to the adenomatous polyposis coli (APC) locus. Am J Hum Genet 1992;51:92-100.
26. Cetta F, Montalto G, Gori M, et al.: Germline mutations of the APC gene in patients with familial adenomatous polyposis-associated thyroid carcinoma: results from a European cooperative study. J Clin Endocrinol Metab 2000;85:286-92.
27. Giardiello FM, Petersen GM, Brensinger JD, et al.: Hepatoblastoma and APC gene mutation in familial adenomatous polyposis. Gut 1996;39:867-9.
28. Gardner EJ: Follow-up study of a family group exhibiting dominant inheritance for a syndrome including intestinal polyps, osteomas, fibromas and epidermal cysts. Am J Hum Genet 1962;14:376-90.
29. Turcot J, Despres JP, St Pierre F: Malignant tumors of the central nervous system associated with familial polyposis of the colon: report of two cases. Dis Colon Rectum 1959;2:465-8.
30. Oldfield MC: The association of familial polyposis of the colon with multiple sebaceous cysts. Br J Surg 1954;41:534-41.
31. Hamilton SR, Liu B, Parsons RE, et al.: The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839-47.
32. Mir-Madjlessi SH, Farmer RG, Easley KA, et al.: Colorectal and extracolonic malignancy in ulcerative colitis. Cancer 1986;58:1569-74.
33. Ekbom A, Helmick C, Zack M, et al.: Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990;323:1228-33.
34. Greenstein AJ, Slater G, Heimann TM, et al.: A comparison of multiple synchronous colorectal cancer in ulcerative colitis, familial polyposis coli, and de novo cancer. Ann Surg 1986;203:123-8.
35. Lashner BA, Turner BC, Bostwick DG, et al.: Dysplasia and cancer complicating strictures in ulcerative colitis. Dig Dis Sci 1990;35:349-52.
36. Ekbom A, Helmick C, Zack M, et al.: Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet 1990;336:357-9.
37. Rubio CA, Befrits R: Colorectal adenocarcinoma in Crohn's disease: a retrospective histologic study. Dis Colon Rectum 1997;40:1072-8.
38. Karnak I, Ciftci AO, Senocak ME, et al.: Colorectal carcinoma in children. J Pediatr Surg 1999;34:1499-504.
39. Gruber SB, Ellis NA, Scott KK, et al.: BLM heterozygosity and the risk of colorectal cancer. Science 2002;297:2013.
40. Eraklis AJ, Folkman MJ: Adenocarcinoma at the site of ureterosigmoidostomies for exstrophy of the bladder. J Pediatr Surg 1978;13:730-4.
41. Densmore TL, Langer JC, Molleston JP, et al.: Colorectal adenocarcinoma as a second malignant neoplasm following Wilms' tumor and rhabdomyosarcoma. Med Pediatr Oncol 1996;27:556-60.
42. LaQuaglia MP, Heller G, Filippa DA, et al.: Prognostic factors and outcome in patients 21 years and under with colorectal carcinoma. J Pediatr Surg 1992;27:1085-90.
43. Jenkinson HC, Hawkins MM, Stiller CA, et al.: Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. Brit J Cancer 2004;91:1905-10.
44. Haddy TB, Mosher RB, Dinndorf PA, Reaman GH: Second neoplasms in survivors of childhood and adolescent cancer are often treatable. J Adolesc Health 2004;4:324-9.
45. Klein G, Michaelis J, Spix C, et al.: Second malignant neoplasms after treatment of childhood cancer. Eur J Cancer 2003;39:808-17.
46. Bhatia S, Sklar C: Second cancers in survivors of childhood cancer. Nat Rev Cancer 2002;2:124-32.