Special Sec ion

In the past thoe than 3 times the number in 1970. As the survivor popu
lation grows, it is increasingly important to address the unique needs of cancer survivors for medical surveillance, continuity of care, and information about how their cancer and its treatment may affect their future health. IJ6J-(h)3(c)-10(a23(r)33()-4(e)33(h)17(.)33(3()20(d)3(d)(o)5( )63(a)5(b)8(o)22)-27

When a tumor is determined to be cancer, this indicates that cells within the tumor have developed the ability to invade into surrounding tissues and to move to remote sites (metastasize) where they can grow and invade. Even after treatment of the original cancer appears to have been effective, cancer cells may persist in the body and eventually grow to the point where they are detected either at or near the site of the original cancer or at a remote site. When this occurs, it is called a recurrence or a metastasis. By definition, a second (or multiple) primary cancer is the occurrence of a new cancer that is biologically distinct from the original primary cancer.[2] The determination of whether a new cancer is a separate primary or a recurrence or a metastasis from the original cancer is important clinically because it influences staging procedures, prognosis, and treatment. This determination usually involves a combination of pathological, clinical and, in some cases, additional laboratory studies. The distinction is easy when pathological information shows that the cancers being compared have different histological features that show that they have originated from distinct types of cells. Clinicians may also use information about typical patterns of recurrence and common sites of metastases for the first cancer. When the answer is not clear cut, molecular and cellular tools may be used to analyze the DNA of cells from the original and the new

The observed number of cancers in a population of cancer survivors divided by the number of cancers expected. The number of cancers expected is calculated using cancer rates from the general population and person-years-at-risk (PYAR) of the survivor population under study. PYAR is counted from the date 2 months after the diagnosis of the first cancer (to exclude multiple primaries diagnosed at the same time) until the date of last known vital status or death, and allocated by age, sex, race, and calendar year. All second and later (third, fourth, etc.) cancer diagnoses are included.

10,000

The EAR is calculated by subtracting the expected number of cancer cases from the observed number, dividing by the PYAR, and multiplying by 10,000 [((O-E)/PYAR) x 10,000]. The EAR represents the number of excess cancers per 10,000 PYAR

tology, behavior (i.e. in situ or malignant), and laterality of paired organs. Multiple primary cancers can either be diagnosed at the same time (synchronous) or at different times (metachronous); coding rules exclude cancers diagnosed within two months of the primary cancer, which are considered to be synchronous cancers, from the multiple primary counts. The coding rules used in this article are those used by the Surveillance, Epidemiology, and End Results (SEER) registries.[3]

Population-based cancer registries are an important resource for studying multiple primary cancers. Registries collect information about each cancer patient in such a way that subsequent primary cancers diagnosed in the same person can be identified. The earliest studies of multiple primaries were done by cancer registries in Connecticut and Denmark.[4] More recently, the SEER Program published a monograph on new malignancies among cancer survivors based on data from the 9 original SEER registries during the 28-year period 1973-2000. The SEER Monograph, with data updated to 2005 (using SEER*Stat software version 6.4.4), is the primary resource for statistics used in this report and will be referred to throughout as the SEER Multiple Primary Study; the monograph can be accessed at http://seer.cancer.gov/publications.[5] The categories of primary and secondary cancer sites are provided in Appendix 2.A and 2.B of the monograph. In some cases, the categories reported for primary and secondary sites differ; for example, the category "acute myeloid leukemia" is used for primary sites and "acute non-lymphocytic leukemia," which includes acute myeloid leukemia and several other categories, is used for secondary sites. More information on the methods used and limitations of the study are provided in the Sources of Statistics section, from pages 17-19.

An estimated 880,300 cancer survivors who have been diagnosed with more than one cancer were living in the US as of January 1, 2005.[6] Among men who have been diagnosed with more than one cancer, the 10 most common primary sites are prostate, colon and rectum, urinary bladder, melanoma, kidney and renal pelvis, oral cavity and pharynx, lung and bronchus, non-Hodgkin lymphoma, leukemia, and thyroid (Figure 1). Among women who have been diagnosed with more than one cancer, the 10 most common primary sites are breast, colon and rectum, uterine corpus, melanoma, lung and bronchus, thyroid, ovary, urinary bladder, non-Hodgkin lymphoma, and uterine cervix (Figure 1). These rankings generally reflect high incidence and survival rates for the first primary cancer rather than unusually high risks for a subsequent cancer. For example, the large number of prostate cancer survivors who have been diagnosed with a multiple cancer reflects the fact that prostate cancer is the most commonly diagnosed cancer in men and has a 5-year relative survival rate of more than 99%, not that prostate cancer survivors have an increased risk of developing additional cancers. (See "What causes decreased risk of developing another cancer?" on page 30.)

The Observed-to-Expected Ratios (O/Es) and Estimated Absolute Risks (EARs) for subsequent cancers for the 15 most common primary cancer sites in men and women are shown in Figure 2. For both men and women, the highest O/Es and EARs are observed for cancers related to tobacco, including cancer of the oral cavity and pharynx, lung and bronchus, esophagus (men only), kidney and renal pelvis, and urinary bladder. Among men, primary sites associated with modest increased risks of subsequent cancer include melanoma, leukemia,

About 1-2% of all cancers are associated with hereditary cancer syndromes; these syndromes are associated with very high lifetime probabilities of developing certain cancers.[7] Individuals with hereditary cancer syndromes have a heritable mutation in every cell, which may have been inherited from a parent or arisen early in development. Even in people with inherited syndromes, the development of cancer still depends on acquiring additional mutations. Many of these syndromes are autosomal dominant, which means there is a 50% chance that someone carrying the gene will pass it to their child. Retinoblastoma, a rare childhood cancer in the retina of the eye, is an example of an autosomal dominant hereditary cancer that is associated with a specific gene mutation in about

predisposition, notably mutations in BRCA1 and BRCA 2 genes, contribute to the excess risk of subsequent cancer among women with early-onset breast cancer. [7]

In addition to genetic predisposition, breast cancer survivors may be at increased risk of developing subsequent

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Colon	12.46*	2.42*	1.67*	1.31*	1.57*	4,487	2,867	12.56
Rectum & rectosigmoid junction	12.24*	2.05*	1.23*	1.17*	1.36*	1,272	937	2.60
Uterine corpus	7.10*	1.54*	1.04	1.12	1.23*	697	567	1.01
Ovary	4.26*	1.42*	1.09	0.76*	1.01	340	338	0.01
ANLL	3.17	0.53*	1.10	1.02	0.99	238	241	-0.02
All subsequent cancers	2.77*	1.22*	1.06*	1.00	1.06*	27,344	25,752	12.34

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	0 (–2, 1)	0- (–2 , 1)	0 (–2 ,210)	(– , 0)	(– 1, 2)			
Colon	7.45*	2.05*	1.40*	1.28*	1.45*	1,621	1,115	9.13Tj/Spans 0 Td7t<FF

Cancers of the colon and rectum are the third most common cancer in men and women in the US, with a 5-year relative survival rate of 64%. The SEER multiple primary study found that most common second cancers among colon cancer survivors are new cancers of the colon and rectum.[21] Among colon cancer survivors, the O/E for subsequent primary colon cancer is 1.57 and for rectal cancer is 1.36 (Table 3). The O/E for all subsequent cancers is highest for colon cancer patients diagnosed with their initial cancer under age 40 (O/E = 2.77) and declines with age, with no overall increased risk among patients diagnosed at age 70 and older. Among patients diagnosed with colon cancer before age 40, the O/E is 12.46 for subsequent colon cancer, 12.24 for subsequent rectal cancer, 7.10 for cancer of the uterine corpus, 4.26 for ovarian cancer, and 3.17 for acute non-lymphocytic leukemia (Table 3).

Much of this increased risk for subsequent cancers among colorectal cancer patients diagnosed at an early age is related to two genetic susceptibility syndromes associated with early onset colon cancer mentioned previously: FAP and HNPCC, also known as Lynch syndrome. Both of these syndromes are inherited diseases in which carrier parents have a 50:50 chance of passing the mutation to each child.[22] FAP is due to an inherited defect that leads to the appearance of numerous (> 100) polyps throughout the large bowel, and usually becomes evident in the second decade of life. If untreated, patients typically develop colorectal cancer at a mean age of 39 years. FAP is responsible for < 1% of colon cancers. The risk of multiple

colon cancers is so high that the recommended treatment is removal of the entire colon at an early age in anyone identified with this syndrome. FAP is also associated with increased risk of cancer of the stomach, small intestine, thyroid, pancreas, and brain. HNPCC is characterized by early onset of predominantly right-sided colon cancer and the tendency to develop multiple cancers. Affected individuals generally develop only a few polyps, and these generally occur at a later age than in patients with FAP.[22] HNPCC families are defined by the occurrence of colorectal cancer in three relatives, one of whom is a first-degree relative of the other two, diagnosis of at least one of the colorectal cancers before age 50, involvement of at least two generations, and exclusion of FAP. HNPCC occurs as a result of mutations in genes that repair errors in DNA and is associated with approximately 3-6% of colorectal

F

Lung & bronchus	3.81*	2.61*	5.03*	3.63*	1.92*	1.83*	1.71*	0.9	1.53*
Oral cavity & pharynx	4.59*	39.85*	12.88*	23.90*	1.32	1.02	0.88	1.47	2.47*
Larynx	7.01*	13.49*	7.22*	13.03*	1.64*	2.01*	1.16	1.56	2.38*
Esophagus	2.46*	28.74*	7.25*	5.50*	1.39	2.38	5.02	3.11	1.78*
Bladder	2.17*	1.00	2.04*	1.07	2.43*	1.64*	18.13*	0.75	1.31*
Kidney parenchyma	1.17*	0.90	0.78	0.59	2.45*	5.50*	0.99	1.31	1.18
Renal pelvis & ureter	2.75*	1.73	3.33	1.10	47.90*	0.45	16.38*	0.36	2.96*
Uterine cervix	2.35*	1.76*	2.98*	1.66*	2.59*	1.11	3.01*	0.61*	1.25*

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Lung & bronchus	2.06*	2.26*	2.73*	2.29*	1.50*	1.58*	1.40*	1.32*
Oral cavity & pharynx	3.82*	18.31*	5.64*	12.50*	1.13	1.13	1.10	2.36*
Larynx	3.39*	5.27*	1.73*	3.63*	1.31*	1.27*	1.34	1.62*
Esophagus	2.05*	12.85*	4.41*	0.76	1.09	0.37	0.84	1.67*
Bladder	1.58*	0.92	1.31*	1.00	0.89*	1.44*	11.00*	1.20*
Kidney parenchyma	0.97	0.69*	0.80	0.73	1.51*	3.98*	1.29	1.17*
Renal pelvis & ureter	1.85*	0.84	1.13	1.26	15.81*	1.05	18.37*	2.44*

Note: Excludes the first 2 months after initial cancer diagnosis. Site definitions are based on Appendix 2a and 2b from Curtis RE, Freeman DM, Ron E, et al., (eds.) *Ne malignancie among cancer r i or : SEER cancer regi rie , 1973-2000*. Bethesda, MD: National Cancer Institute, NIH Publ. No. 05-5302; 2006.

EAR = excess absoute risk per 10,000 person years at risk (PYAR); ANLL = acute non-lymphocytic leukemia.

* p<0.05

vegetable intake.[28] Patients with primary squamous cell carcinomas of the esophagus have a large excess risk for subsequent cancers of the oral cavity and pharynx, and of the larynx. Although HPV infection is the primary cause of cancer of the uterine cervix, increased risks of cervical cancer among smokers have been observed in many studies. HPV infection likely explains elevated risks of some anogenital cancers following oral and pharyngeal cancers and reciprocal excesses of oral cancer following cancers of the anus, cervix, vulva, and penis (data not shown).[25]

Patients with primary cancers of the bladder have a very high (>10-fold) excess risk of developing subsequent cancers of the renal pelvis and ureter with reciprocally elevated large excess risks of bladder cancer among patients with primary cancer of the renal pelvis and ureter (Table 4). Although transitional cell carcinomas of the bladder and

renal pelvis and ureter are known to be strongly related to tobacco smoking, a more modest (1.6 to 2.8-fold) excess risk is observed for subsequent lung cancers among survivors of cancers of the bladder and renal pelvis and ureter.

Primary prevention (tobacco avoidance) and tobacco cessation in smokers is the main strategy to reduce the burden of primary and secondary cancers related to tobacco. The high rates of subsequent primary cancers among patients who have been treated for head and neck and lung cancers led to attempts at chemoprevention. For example, several clinical trials have involved high doses of vitamin A in response to an earlier clinical trial that found that high doses of 13-cis-retinoic acid (vitamin A) were effective in reversing oral premalignant lesions (leukoplakia).[29]

retinoblastoma (O/E=14.89), and Ewing sarcoma (O/E=11.03) (Table 6). Survivors of acute lymphocytic leukemia, the most common cancer in childhood, had a O/E of 4.39; most of this excess is due to subsequent cancers of the salivary glands, brain/central nervous system, bone, and thyroid gland. Cranial radiation given to prevent or treat CNS involvement may be associated with these excesses.[39] The most common types of second cancers occurring among childhood cancer survivors are cancers of the female breast, brain/central nervous system, bone, thyroid gland and soft tissue, as well as melanoma and acute non-lymphocytic leukemia (ANLL).[39] Secondary ANLL commonly develops in association with alkylating agent or topoisomerase II therapy; radiation exposure has also been linked to secondary leukemias, but risks are much lower. Radiation therapy contributes to excess risks for the solid tumors; data on the influence of chemotherapy as a contributor to subsequent solid tumors are more limited. Treatment for these tumors has been modified over the years to maximize efficacy and to minimize long-term risks, including secondary cancer. Secondary breast cancer is most strongly associated with radiation therapy to the chest for women treated between the ages of 10 and 30 years. Breast cancer incidence rates among women with such exposure starts to rise about 8 years after radiation treatment and continues to be elevated for more than 25 years. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography recommend annual MRI screening for women who received radiation therapy to the chest between the

ages of 10 and 30 years. For most women at high risk, the

policy and legislative solutions designed to eliminate cancer as a major health problem. ACS CAN has been an active participant in the development and dissemination of several Institute of Medicine reports that make policy and practice recommendations for addressing the barriers to survivorship care planning, coordination of care, and monitoring of late- and/or long-term post-treatment side effects in survivors. The health policy recommendations in these IOM reports form the backbone for federal bills ACS CAN supports through its advocacy work to promote prevention and care planning for patients as well as

Certain methodological limitations should be considered when interpreting data on multiple primaries from population-based registries and other population groups. Cancer patients are often under closer medical surveillance than the general population, which could lead to earlier detection of asymptomatic cancers that would not have been clinically evident for several years, or pos-

24. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. . May-Jun 2006;56(3):160-167;