Using the Surveillance, Epidemiology, and End Results Database to Investigate Rare Cancers, Second Malignancies, and Trends in Epidemiology, Treatment, and Outcomes

Rare Cancers

The study of rare cancers has been a particularly active area of investigation with Surveillance, Epidemiology, and End Results (SEER) Program data. Although the definition of a rare cancer can be described broadly as a cancer with a low incidence or prevalence, the study of rare cancers is not limited to obscure histologic types that are diagnosed infrequently. It can also include cancers that constitute a rare or difficult-to-study subtype of a more common cancer, such as T4N0 breast cancer. Alternately, rare cancers can be rare occurrences of relatively common histologic types occurring in uncommon locations, such as adenoid cystic carcinoma of the breast. Finally, rare occurrences of common cancers occurring in uncommon hosts, such as male breast cancer, also lend themselves to population-based study using SEER.

Because any single rare cancer affects a low percentage of the population, single institutions are unlikely to treat enough patients to make statistically powerful inferences. Outside of population-based studies, the best options for studying these cancers include case reports, smaller single-institution studies, multi-institution collaborations, or cancer registries dedicated to rare cancer types. Population-based databases such as SEER have the advantage of drawing from a large pool of cases with demographics similar to the general population to accurately characterize the incidence, prevalence, patient demographics, and clinicopathologic features of the disease with high statistical power.

In many instances, SEER studies have been useful by simply describing rare cancer patient populations and by providing population-based demo-

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graphic information like gender, race, and age at diagnosis. Other descriptive information includes distribution of primary site or relative incidence of histology among primary sites.[1] One example demonstrating the ability of SEER to make descriptive observations of rare cancers is a study that identified 2885 cases of dermatofibrosarcoma protuberans (DFSPe) diagnosed from 1973 to 2002.[2] Their observational analysis defined the distribution of primary sites among DFSP patients: 42% occurred on the trunk, 23% on the upper extremity, 18% on the lower extremity, and 16% on the head and neck. Approximately half (57%) were classified as localized, 43% as regional, and <1% as having distant metastases at diagnosis. They found that the incidence of DFSP among blacks (6.5 per million) is almost 2 times higher than for whites (3.9 per million; $P < 0.005$) and that the incidence of the disease increased from 1973 to 2002 by 43% in whites only. Their results refuted previous data that had shown men are more likely to be affected than women, actually showing slightly higher rates in women. This type of descriptive information is easily obtainable from SEER and provides satisfying demographic information compared with other methods, such as single-institutional reports or even multi-institutional clinical trials, which can often include highly selected patient populations.

Another example of using SEER to provide descriptive information about a rare cancer comes from the study by Wright et al,[3] in which SEER was used for scrotal malignancies. They noted that the largest previously published series included only 28 patients, and they were able to compile 471 cases from SEER. The breakdown of the most common histologic types was as follows: squamous cell carcinoma (SCC) (32%), extramammary Paget disease (21%), basal cell carcinoma (18%), and sarcoma (18%). They were able to make some interesting observations about the difference in prevalence and survival between race groups, finding that SCC was more common in black men than in white men (69% vs 31%, $P < 0.001$). They also found a worse survival in SCC compared with other histologic types. Finally, African Americans had a worse survival, with a hazard ratio of 2.

Finally, Grossman et al.[4] used SEER to characterize the distribution of extrapulmonary small cell cancers. They found that 24% were genitourinary, 22% gastrointestinal, 7% head and neck, and 4% breast. They also found that treatment with surgery and/or radiation improved median, 5- and 10-year survival for all stages and sizes.

The results of some SEER-based observational studies have served to confirm the findings of anecdotal reports and small or single-institution studies. Wisnoski et al.[5] reported on a SEER analysis of 672 patients with

acinar cell carcinoma of the pancreas, a subtype that makes up <1% of all pancreatic cancers. They compared survival between acinar cell carcinoma and the much more common adenocarcinoma of the pancreas and confirmed much of what had been shown in smaller studies.[6] Patients with acinar cell carcinoma tended to present at a younger age, were more likely to have resectable disease, and were more likely to undergo potentially curative resection. Their analysis confirmed that the acinar cell subtype of pancreatic cancer follows a more indolent course with a much more favorable long-term survival.

Beyond providing descriptive characteristics, many SEER studies have also helped to define survival patterns of rare cancers. More details about the use of SEER to generate prognostic models are included in a companion article in this issue. The use of SEER to define prognosis for rare cancers is an active area of research. In an example of this kind of analysis, Hennessy et al.[7] were able to characterize the prognosis of patients with sarcomatoid carcinoma of the breast. They found that outcomes in patients with sarcomatoid breast carcinoma were similar to poorly differentiated, receptor-negative adenocarcinoma of the breast. The initial T-stage was a strong predictor of overall outcome. In another example, Bhattacharyya et al.[8] looked at maxillary sinus cancer and validated the tumor, nodes, metastases staging system as an effective predictor of survival. They also showed that SCC portended a much worse survival than adenoid cystic carcinoma, the second most common histology. These examples are just a few of the many studies that reflect the survival patterns of patients diagnosed with these rare cancers in the community at large.

As mentioned earlier, some rare cancers in SEER are in fact common cancers presenting in a patient population in which the cancer type is very uncommon. In one such example that is male breast cancer, the perception has long been that survival is worse among men. To test these and other assumptions about the incidence, presenting characteristics, prognostic factors, and survival rates of male breast cancer, Giordano et al.[9] reviewed male breast cancers using SEER and compared them with breast cancer in women. Among the 2537 cases they identified, they found that men had a higher median age at diagnosis, were more likely to have lymph node involvement, and were more likely to be estrogen receptor and progesterone receptor positive. They confirmed that invasive ductal carcinoma is the dominant histology, accounting for >90% of cases. Lobular cancers were even less common than previously suspected, accounting for 1.5% of cases. Although male breast cancers have been perceived as portending a worse prognosis than female breast cancers,

relative survival by stage was similar between men and women. These observations have been helpful in adjusting providers' opinions of the prognosis and characteristics of male breast cancer.

Trends in Epidemiology, Treatment, and Outcomes

Another important and active use of SEER has been in tracking epidemiologic trends as they relate to cancer. For example, investigators were able to use the San Francisco registry to show an increase in the incidence of Kaposi sarcoma in the early 1980s during the outbreak of acquired immune deficiency syndrome (AIDS).[10-12] These initial reports led to many further confirmatory studies, and the association between AIDS and Kaposi sarcoma has since been characterized and established as general knowledge. Today, the development of highly active antiretroviral therapy has reduced the incidence of AIDS-related Kaposi sarcoma, although this disease continues to serve as an AIDS-defining illness in 2%-3% of human immunodeficiency virus–positive homosexual men.[13] Knowledge of this link has likely led to the diagnosis and consequent treatment of AIDS in many patients, whereas further workup for AIDS might not have been attempted before this association was discovered.

Epidemiologists can also use SEER to examine national and regional trends in the delivery and outcomes of cancer care. State data can be compared with the national SEER cohort to identify increased needs by region. For example, one study compared incidence rates of cancers associated with smoking between Floridians with non-Floridians and found that Floridians had a higher rate of lung and laryngeal cancer compared with the US population as represented by 9 SEER registries.[14] This information is then available for use by public health agencies to consider new policies such as increasing public awareness and/or promoting tobacco or smoking cessation programs. On a larger scale, SEER can be used to track national cancer trends for comparisons of cancer outcomes between the USA and other countries. The results of these studies can help shift federal policies and funding patterns.

Another way SEER can track trends in cancer care is by analyzing practice patterns of community physicians.[15,16] Trends can be identified in the speed of adaptation of national guidelines among community doctors for surgery, radiation, or the sequence of these treatments. In some cases, SEER has been used to show that guidelines are followed for some demographic groups more closely than for others.[17] In one such analysis, Harlan et al.[18] examined the rates of multidrug chemotherapy and adjuvant hormonal therapy among women with node-positive and

node-negative breast cancer in relation to the publication of national guidelines. In this study, SEER was used to identify 8106 women with stage I-IIIA breast cancer, and their treating physicians were contacted by the investigators to verify whether chemotherapy, hormonal therapy, or both were given. The investigators found that adaptation of chemotherapy use for node-negative disease was less complete than for node-positive patients among community physicians over an equivalent time from the release of the National Institutes for Health consensus statement. These and other epidemiologic SEER studies help researchers understand the extent of community physician adherence to national guidelines.

Second Malignancies

Second malignancies have also been a rich area of investigation. The strength of SEER in studying second cancers is the vast number of patients that can be examined over a long follow-up time with the first recorded cases in SEER dating back to 1973. This allows investigators to detect small effects that may not be noted in smaller studies.

Second malignancies are cancers believed to arise from cell lines distinct from those responsible for a patient's first primary cancer diagnosis. One reason the study of second cancers has become more important in recent years is that many cancers are being diagnosed earlier in their progression and in younger patients. This is thought to be because of increased vigilance in screening programs and increased public awareness. Earlier diagnosis has had the effect of increasing the time that cancer survivors live with their cancer diagnosis. Improvements in cancer treatment have also further increased the number of cancer survivors in the population. The expected survival time after diagnosis for many cancers can be years to decades, especially in the case of low-stage disease or other favorable prognostic factors. This increased survival time leads to a higher statistical probability of being diagnosed with a second cancer in a survivor's lifetime even when the cause is completely distinct from the original cancer. It is thought that as many as 10% of all diagnosed malignancies are second cancers.

Cancer survivors are more likely than the general population to be diagnosed with a second cancer for several reasons. Second cancers can be associated with the same genetic factors (eg, BRCA positivity) or environmental factors (eg, smoking) that may have predisposed a survivor to their first cancer diagnosis. Additionally, treatment modalities such as radiation and chemotherapy can result in DNA damage that can lead to mutagenesis and cancer formation later on. Finally, the increased inci-

dence of cancer in cancer survivors may be a result of increased surveillance leading to earlier detection.

Hodgkin lymphoma offers an example of a disease where second cancers are an important consideration in estimating prognosis, especially because many patients are diagnosed young and treatment in the past has included large radiation fields. For long-term survivors of Hodgkin lymphoma, second cancers are a leading cause of death. Travis et al.[19] performed a matched case-control study of patients treated with radiation therapy for Hodgkin lymphoma that were later diagnosed with breast cancer. They found a 3.2-fold risk of breast cancer in patients who received >4 gray (Gy) to the breast compared with those who did not receive radiation to the breast and an 8-fold risk when the dose was >40 Gy. The increased risk persisted as far out as 25 years post treatment. Delivery of >5 Gy to the ovaries actually decreased the risk for breast cancer, and this was postulated to be due to hormone suppression in these women.

The same group of researchers used similar methods to define the increased risk for lung cancer after treatment with radiation and chemotherapy for Hodgkin lymphoma[20] and the risk of leukemia after platinum-based chemotherapy for ovarian cancer.[21] In these cases, geographic population-based registries, some of which are included in SEER, were used as a starting point to identify appropriate patients, whose treatment records were later reviewed for more completeness. Other similar studies have demonstrated increased risks that persist for decades beyond treatment. Megwalu et al.[22] showed an increased incidence of second cancers in the head and neck as well as lung, kidney, and thyroid after the treatment of major salivary gland malignancies. This increased risk extended out to at least 10 years. Travis et al.[23] found that the increase of second primary cancer in men with testicular cancer continues to be at significantly elevated for >20 years after treatment.

Finally, Kleinerman et al.[24] used 13 population-based registries, including some from SEER, to examine second primary cancer after treatment for cervical cancer. They found a 2-fold risk of cancers in the rectum, vagina, vulva, ovary, and bladder in patients treated with radiation. Significant increases of nonchronic lymphocytic leukemia and cancers of the bone and kidney were also linked to radiation therapy. Women treated surgically also had a statistically higher risk of second cancers, and it was postulated that this risk was related to risk factors similar to those of cervical cancer, such as smoking.

Several limitations exist in the ability of SEER to fully define the risk of a secondary cancer caused by radiation or chemotherapy, and these are

covered more extensively in the fifth article in this issue. Briefly, the true rate of second malignancies is difficult to track when patient migrate into or out of areas tracked by SEER. Also, detailed information about chemotherapy is lacking from the SEER database, and information about radiation is limited to whether radiation was given as part of the primary therapeutic regimen. Patient deidentification and follow-up can be performed, but is rarely undertaken except in some of the key articles reported previously. This precludes the possibility of investigating a dose-related response between radiation and secondary tumor formation. Information about the location of the radiation fields is also absent, making it impossible to parse out those second tumors that occur in field, which may be more likely related to previous radiation.

Conclusions

In this review, we have discussed the use of SEER to study rare cancers, track epidemiologic trends, and examine second malignancies. In studying rare cancers, population-based databases such as SEER have the advantage of drawing from a large pool of cases with demographics similar to the general population to more accurately characterize the incidence, prevalence, patient demographics, and clinicopathological features of the disease and with high statistical power. SEER studies have been useful by simply describing rare cancer patient populations and by providing population-based demographic information or other descriptive information, including distribution of primary site or relative incidence of histology among primary sites. Several examples were given of how SEER can be used in this way. SEER is also used to track epidemiologic trends, and these can be contrasted between geographic regions to guide public health efforts or further research. Finally, second malignancies can be studied using population-based registries such as SEER to provide insights into the rates and risks inherent from patient and treatment characteristics.

REFERENCES

1. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100:162-8.
2. Criscione VD, Weinstock MA. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. J Am Acad Dermatol 2007; 56:968-73.
3. Wright JL, Morgan TM, Lin DW. Primary scrotal cancer: disease characteristics and increasing incidence. Urology 2008;72:1139-43.

4. Grossman RA, Pedroso FE, Byrne MM, et al. Does surgery or radiation therapy impact survival for patients with extrapulmonary small cell cancers? J Surg Oncol 2011;104:604-12.
5. Wisnoski NC, Townsend CM Jr, Nealon WH, et al. 672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenocarcinoma. Surgery 2008;144:141-8.
6. Klimstra DS, Heffess CS, Oertel JE, et al. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol 1992;16:815-37.
7. Hennessy BT, Giordano S, Broglio K, et al. Biphasic metaplastic sarcomatoid carcinoma of the breast. Ann Oncol 2006;17:605-13.
8. Bhattacharyya N. Factors affecting survival in maxillary sinus cancer. J Oral Maxillofac Surg 2003;61:1016-21.
9. Giordano SH, Cohen DS, Buzdar AU, et al. Breast carcinoma in men: a population-based study. Cancer 2004;101:51-7.
10. Biggar RJ, Horm J, Fraumeni JF Jr, et al. Incidence of Kaposi's sarcoma and mycosis fungoides in the United States including Puerto Rico, 1973-81. J Natl Cancer Inst 1984;73:89-94.
11. Horn PL, DeLorenze GN, Brown SR, et al. Re: "Temporal trends in the incidence of non-Hodgkin's lymphoma and selected malignancies in a population with a high incidence of acquired immunodeficiency syndrome (AIDS)." Am J Epidemiol 1989;130:1069-71.
12. Reynolds P, Layefsky ME, Saunders LD, et al. Kaposi's sarcoma reporting in san Francisco: A comparison of AIDS and cancer surveillance systems. J Acquir Immune Defic Syndr 1990;3(suppl 1):S8-13.
13. DeVita V. AIDS-related malignancies. In: DeVita V, editor. Cancer: Principles and Practice of Clinical Oncology, vol 8, 5th edition. Philadelphia, PA: Lippincott, Williams, & Wilkins, 2008. p. 2404-7.
14. Lee DJ, Voti L, MacKinnon J, et al. Gender- and race-specific comparison of tobacco-associated cancer incidence trends in Florida with SEER regional cancer incidence data. Cancer Causes Control 2008;19:711-23.
15. Harlan LC, Clegg LX, Trimble EL. Trends in surgery and chemotherapy for women diagnosed with ovarian cancer in the United States. J Clin Oncol 2003;21:3488-94.
16. Mariotto A, Feuer EJ, Harlan LC, et al. Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999. J Natl Cancer Inst 2002;94:1626-34.
17. Potosky AL, Harlan LC, Kaplan RS, et al. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. J Clin Oncol 2002; 20.:1192-202.
18. Harlan LC, Abrams J, Warren JL, et al. Adjuvant therapy for breast cancer: practice patterns of community physicians. J Clin Oncol 2002;20:1809-17.
19. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465-75.
20. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94:182-92.
21. Travis LB, Holowaty EJ, Bergfeldt K, et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med 1999;340:351-7.

22. Megwalu UC, Shin EJ. Second primaries after major salivary gland cancer. Otolaryngol Head Neck Surg 2011;145:254-8.
23. Travis LB, Fosså SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005;97:1354-65.
24. Kleinerman RA, Boice JD Jr, Storm HH, et al. Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer 1995;76:442-52.