A Review of the Definition for Multiple Primary Cancers in the United States

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Highlights and Recommendations

• The definition of a multiple primary has changed over time in the United States.

• Most research on multiple primaries has focused on metachronous tumors, with many studies examining cancer treatment effects on the risk of subsequent primaries.

• The definition and understanding of a multiple primary is often clear to clinicians. However, the information used to make the determination is not documented in the medical record, nor is it available in a pathology report (e.g., distance between tumors, quadrants involved in breast). The difference between multifocal and multicentric tumors of the breast involves assessment of the distance between the tumors.

• Specific changes are needed in the surveillance rules. The definition of “same organ” and “different histology” needs to be clarified with greater precision.

• A flow chart of the sequence or hierarchy of the decisions/rules to determine multiple primary tumors needs to be developed.

• Synchronous tumors arising in the same organ are problematic: they are used rarely in etiologic research; the clinical definition is different from the surveillance definition; the data collection rules are vague; and data quality varies, even among high-quality registries.
   – Site-specific clinical input is needed in the definition.
   – Paired organs should be considered as two separate and individual organs (with the exception that inflammatory breast cancer is one primary because it often occurs bilaterally). Other site-specific exceptions might include ovary and retinoblastoma.

• Metachronous multiple primary definitions are more straightforward than those for synchronous tumors. Areas that need clarification are rules to distinguish differences in site/histology and whether the timeframe (see below) should be revised.

• The 2-month rule to separate synchronous from metachronous tumors needs to be revisited, with a break occurring later and determined empirically (e.g., 4 months or 1 year).

• Assessment of multiple primaries appears to be most difficult for breast cancer; most of the discussion at the meeting about issues, confusion, or definition focused on this site. However, this may have reflected the clinical expertise and general interest of the meeting participants.

• The histologic categories for breast cancer need to be revisited because clinically, many of the histologic types are specific sub-types of intraductal carcinoma.

• Registries must run inter-record edits to improve the data quality of cases with multiple primaries.

• A consensus on training materials is needed to improve their quality and accuracy.
• A multiple tumor indicator may be useful to easily identify cases for multiple primary research studies. An indicator for multicentric and multifocal tumors also may be useful.

• The participants recommended that work on this topic continue. The SEER Program is currently studying the rules for assigning histologic type and as part of this effort, it will be evaluating the current SEER multiple primary rules. It was recommended that the SEER committee evaluating these rules be expanded to include people outside of the SEER Program as well as clinicians from different disciplines.

• A review of the SEER multiple primary rules by the committee pointed out areas that should be clarified/reviewed (numbers refer to rules in the SEER Coding Manual, pg 11+):
  – #1 Add “For a person with no prior cancers, a single lesion…”
  – #3 Change “cancer” to “lesion” – if a new lesion… Second sentence: “If a new lesion…”
    o Revisit the definition of “same histology.”
    o Revisit the 2-month rule.
    o Exception 2: should urinary bladder be excluded?
  – #4 Revisit definitions of same site and different sites. Consider separate site-specific rules.
  – #5 Review the definition of “different histologic types.” For example, which “combination histologies” can be used for multiple histologic types in one lesion, and which ones can be used for multiple lesions?
    o Exception 1: are the four listed histologies the only ones, or are they only examples?
    o Exceptions 2 and 3: These need to be reworded for ICD-O-3, and there needs to be a consideration of multifocal and multicentric versus reporting as separate primaries, especially for breast.
  – #6b Consider rewriting to: “If both breasts contain a lesion, consider these two primaries.” This may not be true for inflammatory cancer of the breast. For what other sites should this be the rule regarding bilateral involvement versus a multiple primary?
  – Lymphatic and hematopoietic – Specify that there is no time rule.

• Feedback to clinicians needs to be created that will enable the retrieval of real-time, conditional (specific patient and tumor characteristics) survival to be more responsive to patient inquiries.
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Welcome and Introductions

Dr. Holly L. Howe, Executive Director of the North American Association of Central Cancer Registries (NAACCR), welcomed participants to the NAACCR-sponsored workshop, A Review of the Definition for Multiple Primary Cancers in the United States. Collecting data on multiple primary cancers is complex, particularly in the United States. It takes time to collect these data, the rules are difficult and cumbersome, and the data often are of poor quality, even when they are from high-quality cancer registries. Questions about the use of these data in research and surveillance have been raised.

Participants were asked to consider the following issue during the workshop: is it important clinically, epidemiologically, and/or etiologically to continue the collection of multiple primary data, as defined by the Surveillance Epidemiology and End Results Program (SEER) and used as a NAACCR standard? This question needs to be considered particularly in terms of:

- New cancer diagnoses following cancer treatment
- The general risk of subsequent cancers in cancer patients (not just treatment-related effects)
- Distinguishing treatment-related risks of subsequent tumors compared with other risks of developing subsequent tumors
- Tumors in the same organ, with the same histology, diagnosed at any time
- The timing interval between the multiple primary diagnoses.

The intent of the workshop was not to create consensus on the most appropriate definitions of a multiple primary, but rather to make consensus recommendations on the directions experts should take in addressing these issues related to the collection and use of multiple primary data. Dr. Howe closed her remarks by thanking the National Cancer Institute (NCI) for their support in sponsoring the workshop.
Multiple primary cancers generally fall into two categories: (1) synchronous, in which the cancers occur at the same time (the SEER definition is within 2 months); and (2) metachronous, in which the cancers follow in sequence (more than 2 months apart) (see Figure 1). Dr. Lynch presented SEER data indicating that from 1973–1999, out of 2.7 million cancers across nine SEER registries, approximately 10 percent of patients developed a second cancer. The actual rate may be slightly higher, because the data collection period does not yet cover a person’s entire lifetime. Little research has been conducted to examine a third or higher number of primary cancers because so few of them occur in the general population. A large population base is needed for research on multiple primary cancers; such a population base will require extensive collaboration between cancer registries.

Causal mechanisms of multiple primary cancers include genes, the environment, treatment effects, and combinations of these three mechanisms (see Figure 2). When researchers focus on genes as causal mechanisms, they often concentrate on cases diagnosed earlier in life (i.e., younger than age 55). Data indicate that when a person is genetically predisposed to develop cancer, he or she more often will do so earlier in life than a person who develops cancer sporadically. A study linking populations from the Utah Cancer Registry, the Genealogical Society of Utah (a database of 1 million Utah descendants), and Utah death certificates found that first-degree relatives of probands were more likely to develop various types of cancers at a younger age than controls. A significant association with the development of cancers also was linked to smoking and alcohol consumption behaviors. [Source: Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 86:1600-1608, 1994.]
Figure 2. Patients with multiple primary cancers: effects of genes, environment, and treatment as causal mechanisms.

As an example of the environment as a causal mechanism, a study from the Connecticut Tumor Registry evaluated the second primary tumor experience of 21,371 patients with oral or pharyngeal cancer in a retrospective cohort study using data from nine SEER registries. The rate of development of second cancers was 3.7 percent per year, and a 20-fold excess of second oral or esophageal cancers was found (a 4–7-fold increase also was found for second cancers of the lung and pharynx). The study concluded that elevated risks of second cancers can be attributable to cumulative tobacco and alcohol exposure. [Source: Day GL, Blot WJ. Second primary tumors in patients with oral cancer. *Cancer* 70:14-19, 1992.]

Treatment effects as a causal mechanism of multiple primary cancers are examined by studying cohorts of individuals diagnosed with a first cancer for which they received treatment (chemotherapy and radiation therapy are most commonly studied). Nested case-control designed studies often are used in these instances. In a study of the treatment for non-Hodgkin’s lymphoma (NHL), an international retrospective cohort of 6,171 patients was examined; approximately 1 in 5 developed a second cancer. The investigators concluded that NHL patients continue to be at significantly elevated risk of developing a second primary cancer for up to two decades following their first cancer diagnosis. Case-control studies of these second cancers are needed to clarify the role of: (1) antecedent therapy (e.g., cyclophosphamide and bladder cancer); (2) shared risk factors (e.g., tobacco); (3) host susceptibility; and (4) other etiologic influences. [Source: Travis LB, Curtis RE, Glimelius B, Holowaty E, Van Leeuwen FE, Lynch CF, Adami HO, Gospodarowicz M, Wacholder S, Inskip P, Tucker MA, Fraumeni, Jr. J, Boice, Jr. JD. Second cancers among long-term survivors of non-Hodgkin’s lymphoma. *J Natl Cancer Inst* 85:1932-1937, 1993.]

The WECARE Study, an ongoing international matched case-control study, was highlighted to illustrate an approach to examining the combined effects of genes, environment, and treatment as causal mechanisms of multiple primary cancers. The study’s hypothesis is that radiation treatment administered to a patient who is heterozygous for the ataxia telangiectasia mutation gene will increase the risk of developing invasive or *in situ* contralateral breast cancer. Results of this study are pending.
The challenges associated with studies on multiple primary cancers are:

- The accuracy of cancer registry information. (This includes completeness of case finding and follow-up and the ability to separate initial primary cancers from subsequent new primaries.)
- The availability of medical record information. (Studying the effects of treatment requires detailed information, often from archived records or worse yet, destroyed records.)
- The need for a large population base. (This often requires collaboration of several central registries.)
- Long-established registries are favored. (It often takes time for multiple primary cancers to occur.)
- Population mobility. (In the United States, central registries can be responsible for following a cancer patient for life, but they only are responsible for following cancer incidence experience while the patient is resident of the geographic coverage area; this leads to an underestimation of the standardized incidence ratio.)
- Survival bias. (This can occur when cancer survival confounds exposure; for example, when live patients are needed to test a genetic hypothesis.)
- The availability of pathology tissue. (Sometimes a biologic sample is desired, but often it is difficult to obtain tissue in sufficient amounts.)
- Intensive labor requirements to perform studies.

Despite these challenges, multiple primary cancer studies are important, powerful approaches to evaluating genes, environment, and effects of treatment; they also provide a unique role for population-based cancer registries in this research.

**Discussion**

In discussion, it was noted that colon cancer patients who develop a second colon cancer at another subsite may already have been developing this second tumor when the first one was detected (it takes approximately 10 years for colon tumors to develop). Researchers keep this in consideration, and the longer the time period between first and second tumors, the more confident researchers are that they are in fact dealing with a separate cancer. One of the challenges facing clinicians and researchers is that limited medical information is available for some patients regarding their cancer diagnosis. In most cases, clinicians are left to make treatment-related decisions based on the management used to establish the diagnosis. It is not always clear what is going on biologically based on the available information.

Cancer registries in Sweden and the Netherlands define second primary cancers differently than the United States, particularly with respect to the leukemias and lymphomas. Some meeting participants voiced concern that Dr. Lynch’s data may underestimate the risk of nonlymphocytic
leukemias following NHL because of the way certain second primaries are counted in the United States. Some participants also noted that the differences in definitions might affect the results of these studies. Dr. Lynch noted that in designing the studies, the risk of developing cancer was evaluated by individual country, so the expected number of cancers was country-specific based on the definition used in each country. Nevertheless, some cases may be missed.

Although it makes sense to select young people for inclusion in these studies because they can be followed for long periods of time, younger people who develop cancer may be genetically predisposed and different from older patients who may not have a genetic predisposition. The WECARE Study will sample participants’ DNA to determine whether younger patients are more predisposed. Researchers intentionally limited WECARE Study enrollment to subjects under the age of 55 years to increase the likelihood that subjects would have a genetic predisposition to developing cancer. One participant asked about the data obtained from cancer registries, particularly whether all cases are used. Dr. Lynch noted that a great deal of information on metachronous tumors is used, but very little information on synchronous tumors is used.

**History and Overview of Multiple Primary Rules**

**John Young**

An overview of the evolution of expert thinking about multiple primary cancers was presented. The *First National Cancer Survey* (1938) had no mention of multiple primary cancers, and leukemia and NHL were not considered to be cancers at this time. The *Second National Cancer Survey* (1948) also did not mention multiple primaries, but it did include NHL and leukemia as cancers. The *Third National Cancer Survey* (1969–1971), published as an NCI monograph, did not document rules for defining multiple primaries, but instructions for documenting the number of patients and the number of cancers was provided.

The American Cancer Society’s *Manual of Tumor Nomenclature and Coding* was used for cases diagnosed in August 1973 and later. The system utilized a three-digit code for histology, a reportable-by-agreement list that included benign brain and polycythemia vera, special rules for bladder cancer, and also included basal and squamous skin cancers. Cancer was defined as any malignant neoplasm. In 1974, all *in situ* and malignant tumors were designated as reportable.

In 1974, the *SEER Program Code Format* was published. This document provided some definitions and had specified fields for sequence number, paired organ involvement, and multiplicity. The first written multiple primary rules appeared in 1975, but did not include a timeframe. In 1976, the first *SEER Code Manual* was published. The document revised multiple primary rules and included the first mention of time (“if a new independent primary cancer of the same histology as the earlier one is diagnosed in the same site at a later time”) related to multiple primary cancers, although the phrase “at a later time” was not defined. In 1977, the reportable-by-agreement list was dropped. In 1979, new rules for defining multiple primary cancers were released. The first definition of synchronous primary tumors (“within 2 months”) appeared in 1979, as did more specific rules for breast cancer and other paired organs. In a departure from other countries’ rules, the decision was made that every segment of the colon should be considered a different primary site.
The second edition of ICD-O changed the definitions of primary site in 1988, and the 1992 \textit{SEER Program Code Manual} included a new definition of primary site based on changes that appeared in ICD-O-2. ICD-O-3 included a new set of hematopoietic diseases, and presented new rules for determining multiple lymphomas and hematopoietic diseases. An incomplete definition of primary site was published in tables in the ICD-O-3 book (sites C56 and C57 were missing). A new complication for 2003 is that the American College of Surgeons Commission on Cancer Manual, \textit{Facility Oncology Registration Data Standards} (FORDS), states that: “each occurrence of melanoma of the skin is a new or separate primary unless a physician states otherwise.” Central registries, therefore, will receive melanoma cases from hospital registries that will be coded as multiple primaries even though they do not actually meet the central cancer registry definition of multiple primary cancers.

The World Health Organization’s International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries primary rules do not depend on time; and only one tumor (depending on histologic group) per organ or pair of organs per person per lifetime is reportable. These rules are different from SEER rules.

Two NCI publications—\textit{45 Years of Cancer Incidence in Connecticut} and \textit{Multiple Primary Cancers in Connecticut and Denmark}—were discussed. \textit{45 Years of Cancer Incidence in Connecticut} examines the number of people and the number of primaries that occurred from 1935–1979 in that state. During that period, the number of patients with more than one primary was reported as 5.9 percent. The SEER monograph \textit{Multiple Primary Cancers in Connecticut and Denmark} republished Connecticut’s data, expanded coverage from 1935–1982, and used a slightly different definition of cancer. The 2-month rule was applied to the definition of multiple primary cancers. Of the individuals who had multiple primaries, 20 percent were synchronous and 80 percent were metachronous. Overall, approximately 10 percent of patients had more than one cancer. In general, the percentage of individuals with multiple primary cancers increases over time, and is influenced by the definition of site and type, as well as by improving survival times and treatment.

Arguments for maintaining the current SEER definitions of multiple primary cancers include the following:

\begin{itemize}
  \item Registrars may do things differently and may count too many tumors, but it is better to count too many than too few, because it is often possible to omit subsets of tumors for analysis.
  \item By using the current rules, a unique group of patients are identified (e.g., allowing a woman to have what is considered more than one breast cancer at a time identifies her uniquely; this is not possible under international rules).
  \item Consistency over time.
  \item The rules do not involve too many patients.
\end{itemize}
Arguments for changing the rules defining multiple primary cancers include:

- The rules are too complicated.
- It is difficult to achieve consistency.
- The United States is not consistent with international rules.
- The current rules may overestimate the true incidence of cancer.
- The rules do not make sense from a clinical standpoint, especially the 2-month definition.

**Multiple Primaries: Clinical Perspectives**  
**Stephen Edge**

Few clinicians know about issues surrounding the coding of multiple primary cancers, because these rules do not impact their clinical practice of medicine. A multiple primary cancer can be defined as having two primary cancers in the same organ at the same time. Multiple primaries can have an impact on cancer treatment (e.g., surgery), including the extent of the treatment for a known local primary. Synchronous cancers can lead to a different course of treatment. Registrars should expect to see an increased frequency of multiple primaries in the coming years, as awareness of multiple primary cancer syndromes (e.g., hereditary nonpolyposis colorectal cancer), use of screening (especially for breast and colon cancers), and sensitivity of screening in organs susceptible to multiple primary cancers all increase. Some of the advanced screening technologies include breast MRI, PET scanning, and virtual colonoscopy.

In terms of breast cancer, patients can have synchronous multiple primaries, including multicentric cancer of the same breast, synchronous contralateral breast cancer, and metachronous contralateral or ipsilateral tumors. In many of these cases, a decision must be made if these are ipsilateral recurrences or new primaries—this issue may have an impact on the primary treatment. Generally, contralateral breast cancers are new primaries; they are not metastases. The incidence of contralateral breast cancer is approximately 8 percent among patients who do not have inherited susceptibility to breast cancer (the inherited susceptibility risk of developing contralateral breast cancer may be as high as 40–50% by age 70).

Defining multicentric versus multifocal cancers for cases of synchronous ipsilateral breast cancer using medical records is almost impossible. Clinicians generally consider multicentric cancers of the breast as having separate histologies or separate quadrants separated by 5 centimeters (cm.) or more. Multifocal cancers generally occur in the same region.

Ductal extension some distance from a primary breast cancer is common. Islands of tumor cells can be seen throughout the breast in cases of intraductal lesions. Researchers have injected mastectomy specimens with a latex to highlight the paths of ducts and generate three-dimensional reconstructions of the breast and have found a large proportion of patients with a focus of cancer distant from what was defined as the primary tumor. It is possible to have a focus of *in situ* cancer 3 or 4 cm away from the primary tumor. Researchers at The University of Texas...
M.D. Anderson Cancer Center published a paper examining the characteristics of unicentric versus multicentric cancer among patients who had a mastectomy. They found that 60 of 284 had multicentric cancer; no differences related to family history, age, etc. were identified. [Source: Katz A, Strom EA, Buchholz TA, Theriault R, Singletary SE, McNeese MD. The influence of pathologic tumor characteristics on locoregional recurrence rates following mastectomy. *Int J Rad Oncol Biol Phys* 50(3):735-742, 2001]

A true multicentric cancer may be considered a contraindication to breast-conserving surgery. The general clinical rule is that if the surgeon can get all the way around the tumor, no other mammographic lesion is present, and the margins are negative, then the outcome is the same whether it is an extended intraductal lesion or not. Regarding contralateral breast cancer, a metachronous second primary is a new primary, regardless of the timing. In ipsilateral cancer, the risk of a new primary is probably the same, although no data exist to support this hypothesis. Patients undergoing breast-conserving surgery are just as likely to develop an ipsilateral breast cancer as they are a contralateral breast cancer. Initially, most ipsilateral events represent a true recurrence; late ipsilateral cases are very likely new primaries, but this determination is difficult to make. Generally, clinicians consider cancers to be a recurrence when they arise in the same quadrant of the breast or the same site as the primary.

Are ipsilateral breast events recurrences or new primaries? One recent study defined new primaries as different histologies or different locations in the breast, and recurrences as the same histologies or the same locations in the breast. In the study, a total of 136 out of 1,152 patients had an ipsilateral event over 14 years; 60 of them were defined as recurrences and 70 were defined as new primaries (6 could not be classified). The 10-year disease-free survival rate for women who had a recurrence was 40 percent; the cause-specific survival rate was 55 percent. Among women who had a new primary, the disease-free and cause-specific survival rates were 85 percent and 90 percent, respectively. [Source: Smith TE, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Rad Oncol Biol Phys* 48(5):1281-1289, 2002.]

The number of patients with multiple breast primary cancers also will increase with increased use of genetic testing for breast cancer, awareness, and marketing. Technological advances (e.g., ductal lavage, ductoscopy) will lead to increased quality of screening and improved risk prediction. Many problems are associated with defining a second primary cancer and distinguishing it from multifocal disease, particularly in the breast. The impact of a second primary cancer on therapy needs to be carefully considered, as does the risk of developing a second primary cancer resulting from the therapy for a first primary cancer. Molecular genotyping of cancers eventually will revolutionize the way patients are treated and will allow clinicians to individualize therapy. It will help clarify the patients who will develop a recurrence from those who will not.

**Discussion**

It was noted that research is abundant in describing genetic changes in tumors, particularly with regards to examining use of p53 mutation analysis or loss of heterozygosity to determine whether
a second lung cancer or second head and neck cancer may be derived from the same clone. These approaches are still in the experimental stage. Dr. Edge was asked if genetic-based approaches are likely to become clinically useful and help differentiate whether multifocal cancers are likely to be independent or not. Dr. Edge explained that molecular genotyping of cancers likely will revolutionize the way clinicians treat patients. It will enable individualized therapies and will identify patients whose disease will recur and those whose disease will not. It is not clear whether molecular genotyping will allow clinicians to determine whether two tumors thought to be the same were derived from a monoclonal origin. He added that this revolutionary technology also probably will not help to clinically define multiple primary cancers, and voiced skepticism that molecular phenotyping of tumors to individualized therapies will affect clinical care in the next 10–15 years.

It was noted that in the past, registrars have taken the word of the physician to be the final and ultimate decision. The Collaborative Staging System, however, has changed this and has empowered the registrar for determining stage and disease progression information. New training will be needed for registrars if the definitions provided in Dr. Edge’s presentations are adopted. A number of participants voiced support for adopting these definitions. Dr. Edge noted that a convention for codifying situations in which, for example, patients who have a breast tumor are found to have a second cancer in the same breast 3 months after diagnosis of the first tumor. The registry convention for determining whether a cancer is a second primary is 2 months, although participants discussed other periods of time, and noted that a 4-month rule would be consistent with SEER staging rules. Whatever rule is adopted, Dr. Edge emphasized the need to be consistent in applying the rule and recognize the limitations of the data when they are reported.

If a patient has a cancer diagnosed at an early stage and a subsequent cancer is detected, it is more likely to be a second primary than a recurrence. When advanced cancers are diagnosed, however, it is unclear whether subsequent cancers in the patient are more likely to be a recurrence or a second primary. Dr. Edge noted that the definition of multicentric used by registrars would include multiple primary cancers according to the definition used by clinicians, and that the definition of multifocal cancers used by registries would not include multiple primary cancers as defined by clinicians.

Detection and Reporting of Multiple Primaries
Eric Holowaty

Ontario has eight Cancer Planning Regions, each with a specialized oncology treatment center. All radiation oncologists and about 70 percent of the province’s medical oncologists are based in these centers. Most surgical oncologists and other surgeons performing cancer surgery are not based in these centers; rather, they are practicing out of approximately 200 public hospitals across Ontario. About one-half of all patients who have been diagnosed with new primaries pass through Ontario’s specialized treatment system; these patients are placed under much closer post-treatment surveillance than patients never referred to these Centers. Typically, these cancer patients are seen at 6-month intervals for the first 5 years following diagnosis and at yearly intervals thereafter.
About 15 years ago, IARC published a study on the risk of second primaries following cervical cancer treatment. The inception cohort consisted of approximately 90,000 women diagnosed with cervical cancer. The risks of second primaries across participating Canadian provincial cancer registries were substantially more variable than the risk of first primaries in these same provinces. For example, nearly a twofold difference was found in the risk of second primaries (all sites combined) in the province with the highest rates compared with the province with the lowest, and only a 10 percent difference in risk of first primaries across all provinces (again, all sites combined). It is hypothesized that post-treatment surveillance could introduce an appreciable lead time or other bias in detecting subsequent neoplasms and thereby confound the research community’s ability to accurately estimate the risk of second primaries following a first primary.

Multiple tumors are defined as two or more discrete cancers that are not the result of metastasis or recurrence and are independent of each other. Unfortunately, no consensus has yet been achieved across cancer registries, or among clinicians or researchers for that matter, on the definitions of multifocal and multicentric cancers and whether or not they differ. And unlike first primaries, detection of second or later primaries often relies on the degree of post-treatment surveillance.

Registries face a number of challenges in registering a second cancer. A common problem is determining whether a second lesion in a different location from the first but with the same, similar, or unknown morphology is an independent primary. Another example is determining whether a second lesion in the same organ or tissue has a morphology that is different enough from the first lesion to be considered a separate primary. The basic rules at the Ontario Cancer Registry for the registration and reporting of second primaries are more stringent than the SEER rules, and even the IARC rules, and are as follows:

- Two reports of possibly discrete tumors in the same patient are only considered independent primaries if they arise in different organs and if the morphologies are both known and distinct.
- All other reports are considered possibly multifocal and registered only once.
- No distinction is made between synchronous and metachronous tumors.

The Ontario Cancer Registry collects and summarizes records electronically. A computer decides whether sufficient evidence exists to register a second independent primary and if so, what site, what morphology, what date of diagnosis, etc. The rate of second primaries in the Ontario Cancer Registry was 6.2 percent in 2000, a rate somewhat lower than that estimated by SEER.

Of importance, the cumulative likelihood of being diagnosed with a second breast primary was 53 percent higher among women with follow-up through Ontario’s specialized oncology system. Overall, the likelihood of being diagnosed with a second primary in any solid organ following diagnosis of a first primary is up to 40 percent higher among patients seen through Ontario’s specialized system than among cancer patients never referred to these centers. The cumulative
likelihood of being diagnosed with a second cancer is increasing, and this effect appears to be independent of whether patients are seen at a specialized treatment center.

Uses for second primaries registered in cancer registries include:

- Estimating the risk of second cancers among cancer patients in terms of temporal and geographic comparisons
- Etiologic studies and information on hereditary influences, common exogenous causes, and treatment-related effects
- Health services research
- Prognostic indicators.

**Discussion**

Several participants expressed skepticism that post-treatment surveillance could result in such a significant difference. Dr. Holowaty noted that the data are age standardized, and are controlled for date of diagnosis and treatment. He explained that the cumulative likelihood of being diagnosed with a second cancer increases somewhat over time, and that this effect appeared to be independent of whether patients were first seen at a specialized treatment center. Patients referred to the specialized treatment centers tended to be slightly younger and to have more advanced disease. Dr. Holowaty expressed a belief that the differences noted in his results were attributable in large part to surveillance issues. The system for registering cancers in Canada does not rely on physicians reporting follow-up information; rather, it relies on medical record abstraction, regardless of whether the cancer was managed at a specialized treatment center or a public hospital. One participant noted that this system may miss a significant number of cancers managed in physicians’ offices, where most cancer follow-up traditionally is conducted. If the cancer is not confirmed pathologically, the Canadian system may not identify the case as a cancer. Similarly, if the patient is not referred to outpatient surgery or to a specialized treatment center for radiotherapy or systemic treatment, the system will not identify these cancers. Dr. Holowaty noted that these are possible confounders or sources of bias to the data he presented.

Dr. Holowaty also explained that there may be an appreciable surveillance bias in the detection and reporting to a cancer registry of second primaries, reminding participants however that his analysis was restricted to Ontario. Dr. Holowaty and colleagues do not have access to medical billing records outside of the Ontario specialized system. They are trying to obtain access to such records, but the Canadian government is reluctant to release them. A participant expressed belief that researchers may see a lead time if they conduct more intensive surveillance, but it will not change the rate of detection of second primaries, unless the patients are dying before they develop their second primary.
Working Group Discussion

Workshop participants were assigned to one of the following working groups: Etiology, Epidemiology, or Clinical. Each group had a facilitator and recorder to capture the salient points of discussion. The working groups were asked to answer a series of questions related to the biology, history, and clinical significance of multiple primary cancers based on the perspective of the group to which they were assigned. Table 1 summarizes the responses of the working groups to these questions.

Table 1. Working group responses to questions on the biology, history, and clinical significance of multiple primary cancers.

<table>
<thead>
<tr>
<th></th>
<th>Etiology</th>
<th>Epidemiology/Surveillance</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Is the collection of multiple primary tumors, as used by U.S. registries, important?</td>
<td>Yes, particularly as patients live longer after treatment, and especially for cancers diagnosed in children and young adults (e.g., testicular cancer, Hodgkin’s disease).</td>
<td>Yes, particularly in terms of disease burden and prevalence.</td>
<td>Clinicians do not consider the rules for coding multiple primaries; their perspective is different than the surveillance community’s perspective.</td>
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<td>It can be a springboard for more investigations to examine trends in specific types of cancers over time. Indicator variables could be developed; this is more of an issue for synchronous primaries than for metachronous primaries.</td>
<td></td>
<td>The management of multiple primaries, especially those presenting in close time intervals, will be highly variable, and will be influenced by stage of each disease, prognosis, and the perception of each cancer’s short- and long-term consequences.</td>
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<td>Data on synchronous primaries have been used far less than data on metachronous primaries.</td>
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<tr>
<td><strong>Etiology</strong></td>
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<tr>
<td>Is it an initiator, a new cancer, or can it function as a promoter (e.g., some data suggest that treatment functioned as a promoter in regard to lung cancer following Hodgkin’s disease in a set of smokers)?</td>
<td>Site, histology, laterality, and date of diagnosis information are important. The data collected can be used for a variety of different functions.</td>
<td>Collecting data on all primaries in different organs, regardless of timing, must be continued.</td>
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<tr>
<td>User-friendly tools for examining the ability to compute standardized incidence ratios (person years per second cancers) are needed.</td>
<td>Much of these data are used for survival analyses, and they can be used to calculate the risk of a second primary after a first primary.</td>
<td>Collecting information on different primaries in the same organ also is needed, including consideration of site-specific characteristics (e.g., the amount of separation between tumors, stage/other prognostic factors).</td>
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<tr>
<td>Little is known about the quality and completeness of second primary case ascertainment.</td>
<td>Should multiple tumors be used to calculate risk?</td>
<td>Stage and prognostic factors are of primary importance.</td>
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<td>Synchronous tumors often are ignored, except for defining incidence burden.</td>
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<tr>
<td><strong>What multiple primary information is important?</strong></td>
<td><strong>Is the interval between these tumors important? Is it specific to specific tumors? Which ones?</strong></td>
<td><strong>Yes, the interval is important for all tumors, particularly for looking at the late effects of treatment.</strong></td>
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<td>It may be useful to parcel the intervals into short and longer periods to see what the trends look like in relation to chemotherapy and radiation therapy.</td>
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<td></td>
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<td>The interval is not specific to specific tumors.</td>
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<tr>
<td></td>
<td></td>
<td>Yes, it is very important, especially for the same-site, same-histology tumors.</td>
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| | | Yes, it is important to note the time of each in terms of the impact on treatment. With synchronous tumors, clinicians might not be able to treat them both at the same time because the treatment for one may have competing toxicities for treating the other. The interval is important, but probably not as clinically significant as the impact of treatment.
<table>
<thead>
<tr>
<th>If so, is the interval (± 2 months) appropriate?</th>
<th>Etiology</th>
<th>Epidemiology/Surveillance</th>
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<tr>
<td>The reasoning or scientific rationale (if there was one) for the 2-month interval is unclear. It likely was an arbitrary decision so that there was a consistent rule. One might question whether collecting synchronous tumors is important because they are not studied very often. However, if two tumors are diagnosed on the same day, the question would be which one should be recorded?</td>
<td>The 2-month interval seems to be too short. The field may be allowing an increased ability to detect tumors over time drive this issue. It is unclear what the best interval should be, but 1 year might be a more appropriate interval.</td>
<td>The interval could extend to 4 months to agree with Collaborative Staging, or could be eliminated altogether. Site-specific rules may be needed. The time interval between two same-site primary cancers is not important in distinguishing a multiple primary from a multifocal cancer. The definition of multifocal versus multicentric will be a site-specific question.</td>
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<tr>
<th>Does histology matter if the tumor occurs in different organs? The same organ?</th>
<th>Etiology</th>
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<th>Clinical</th>
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<tbody>
<tr>
<td>Yes, the histology matters in both cases. Etiologically, more research should be conducted at the level of histologically specific tumors, rather than at the site-specific level. However, experts may not have the ability to exploit this area of research yet.</td>
<td>Yes, histology is an indication of the independence of the primary. Researchers used to use information on the <em>in situ</em> present in all the lesions as an indicator of whether they are independent primaries. Now, they often look at mixed histologies that can be counted as a single primary in some instances.</td>
<td>Yes, in different organs, because it sometimes influences treatment, but it is difficult to determine and in some cases may not be helpful in the same organ. A mechanism is needed for defining metastatic versus different primaries, but one cannot assume two cancers are both metastatic just because they are the same histologic type.</td>
<td></td>
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<tr>
<th>Does the tumor sequence matter whether the tumors occur in the same organ? In different organs?</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Yes, for both situations. The concept of studying different combinations of tumors and the sequence in which they occur has relevance.</td>
<td>Yes, sequencing is important, and it is important in analytic studies to know the cancers that can be associated (e.g., colon and a lung, colon and an ovary). Importantly, tumor sequence also gives the ability to retain flexibility in analyses.</td>
<td>Yes and No. It matters for treatment, but not for how tumors are coded.</td>
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</table>
### Etiology

For prognosis, both are important, this relationship could vary by site.

### Epidemiology/Surveillance

Yes, but it is difficult to obtain information on recurrence and relapse as opposed to multiple primaries. Many of the tumors being counted as multiple primaries may actually be recurrences. The definitions are difficult to apply.

### Clinical

Yes. There will have to be site-specific definitions for whether it is a recurrence or a new primary.

<table>
<thead>
<tr>
<th>Question</th>
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<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is relapse/recurrence more important information than multiple primary for predicting outcome (death)?</td>
<td>For prognosis, both are important, this relationship could vary by site.</td>
<td>Yes, but it is difficult to obtain information on recurrence and relapse as opposed to multiple primaries. Many of the tumors being counted as multiple primaries may actually be recurrences. The definitions are difficult to apply.</td>
<td>Yes. There will have to be site-specific definitions for whether it is a recurrence or a new primary.</td>
</tr>
<tr>
<td>Is a short interval between two tumors in the same organ really a new primary? A recurrence? A relapse? Or part of the same first primary?</td>
<td>It depends on the location of the tumor. Over a short time, it is more likely to be a progression than a recurrence. The interval between the two tumors by itself does not answer the question.</td>
<td>All of these are possibilities.</td>
<td>This is a site-specific issue.</td>
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### Section II: Collection and Quality Issues

**NAACCR Record Consolidation Committee**

**Frances Ross**

NAACCR’s Record Consolidation Committee, an ad hoc committee appointed in April 1997, was charged with: (1) examining existing principles and approaches to record consolidation, and (2) developing recommendations and guidelines for best practices for performing record consolidation. Record consolidation is an essential function of central cancer registries. The process was designed to ensure that each primary cancer is counted only once and that the information stored is the best information available from all sources. In central registries, multiple source reports from hospitals, outpatient clinics, pathology reports, laboratory reports, etc. describe many different patients. These patients may have one or more primary cancer after a registry’s record consolidation process is carried out.

Record consolidation is necessary to: (1) accurately count the number of new cancer diagnoses in a population, (2) consistently count cancer diagnoses in different populations for comparison purposes, (3) appropriately identify synchronous and subsequent primary malignancies in the same person, and (4) accurately describe patients and tumors for cancer control and cancer research purposes. The Record Consolidation Committee defined standard terms (i.e., source record, patient, tumor, facility, patient linkage, tumor linkage, and consolidation). It also examined the process of record consolidation within the context of different central registry environments (the process is unique at each central registry) and identified issues that affect quality of the data (e.g., unique population characteristics, quality of reporting sources, legislation, available resources, etc.).
The Committee identified the following essential processes of record consolidation: (1) patient linkage, (2) tumor linkage, and (3) consolidation of best data values. Most registries utilize a combination of automated and manual record consolidation. Required elements for automated record consolidation include edit checking to ensure accurate records, rules or standards by which to identify individual patients and individual tumors, and rules to determine best data values. In 1999, the Committee submitted a report to the NAACCR Board that recommended a feasibility study to measure the impact of different record consolidation methods on tumor counts. [Source: NAACCR Record Consolidation Committee. Central Cancer Registry Record Consolidation: Principles and Processes. Sacramento (CA): North American Association of Central Cancer Registries, July 1999.]

The Committee studied the feasibility of conducting a test among central registries to determine whether they are counting tumors consistently and accurately. The feasibility study concluded that a record consolidation test was possible, but with the following caveats: limited scope and additional resources. The test should be restricted to tumor linkage and consolidation (not patient linkage); to SEER multiple primary rules (not IARC); and to using NAACCR Version 9 records, ICD-O-2 codes, and diagnoses dates from 1998–2000. The additional resources included hiring a Project Director, paying contractors to develop test records, paying alpha and beta testers, providing technical support for creating and running the test, and providing expertise for analyzing the results of the test. The feasibility study results were submitted to the NAACCR Board and in November 2000, NAACCR was awarded an NCI contract that included monies to carry out the project.

Approximately 1,000 source records were desired, and these were created by four contractors. Three experts from SEER registries were recruited to create a gold standard file of consolidated records. In December 2001, the input test file and the gold standard file were finalized. After the alpha test was conducted in February–March 2002, two beta tests were conducted in state cancer registries. Nine additional registries were selected, with beta tests beginning in January 2003.

The preliminary results from the first three tests were discussed. A total of 661 input source records representing 280 patients were developed and used in testing the registries. One registry reported nine fewer tumors overall than the gold standard; however, this difference included 25 persons who had fewer tumors and 18 who had more tumors, for a total of 43 misclassified tumors. The second registry reported 13 fewer tumors than the gold standard, and this involved 13 persons with fewer tumors and 2 with more tumors, for a total of 15 misclassified tumors. The third registry had exactly the same number of tumors as the gold standard; however, 13 people had fewer tumors and 13 had more tumors, a total of 26 misclassified tumors. Within broad categories of cancer types, accuracy and consistency varied; for example, overall counts for the digestive system may have been close, but tumor counts for individual sites such as stomach, esophagus, colon and rectum could be further off. Across categories, experts were more likely to assign tumors to the ill-defined site category than the registries. These test results show inconsistent application and interpretation of multiple primary rules. Inconsistent application of these rules could have important implications for: (1) calculating incidence rates accurately, (2) comparing rates among central cancer registries, (3) identifying appropriate records for research studies, and (4) evaluating synchronous and subsequent malignancies in a population. Remaining activities for the Record Consolidation Test Project include conducting the test in nine more
registries, analyzing the results in more detail, presenting the findings at the NAACCR Annual Meeting, and developing an automated method for any registry to perform the test and receive comparison feedback.

Discussion

Participants’ opinions differed as to whether the number of misclassification errors was troubling. Although some would only be satisfied with perfection or near-perfection, others believed that the proportion of errors was small, resulting in useful and fairly reliable data. Furthermore, although the discrepancies may not be significant in total, they could represent a larger problem for specific cancer sites. Overall, the registries tested were 98 percent accurate in correctly identifying tumors. It appears that the tumors that were problematic for the experts also were problematic for the registries. Ms. Ross noted that the registries were aware of the opportunity to conduct followback using a Web site specially created for the project. She believed that registries had taken advantage of this opportunity during their followback activities.

In response to a question about whether it was possible to rate the registries in terms of concordance with IARC rules, it was noted that two cancer registries in England, both of which use IARC rules, are hoping to take the test to examine this issue.

The more source reports a registry receives on a cancer, the higher the likelihood of miscounting because source reports may include incorrect diagnosis dates, inaccurate site histology, and may lead registrars to believe the report reflects a new tumor, when in actuality it is not. Ms. Ross and colleagues examined three registries (the Kentucky Cancer Registry, the Cancer Surveillance Program of Orange County, and the Minnesota Cancer Surveillance System) that volunteered to count the number of source reports per tumor and the number of tumors per patient in their data. In calculating these numbers for a 2-year period, it was found that although variation occurred in the numbers of reports per tumor, a consistent ratio was found for tumors per patient. Participants noted that it may be interesting to compare the ratio of tumors per patient for specific cancer types/sites (e.g., melanoma).

The New York Experience With Two Sets of Multiple Primary Rules

Maria Schymura

The New York State Cancer Registry has been actively maintaining two multiple primary cancer systems using two sets of multiple primary rules since 1996: IARC rules and modified SEER rules. The advantages of using conservative tumor ascertainment for New York using the IARC rules include consistency with historical reporting and a tendency to avoid misclassification. The IARC rules also tend to be easier to implement and can yield unambiguous rate statistics. The registry also adopted SEER rules so that its data are compatible with SEER and with other state registries. Implementation of SEER rules also is required by the Centers for Disease Control and Prevention’s National Program of Cancer Registries. The registry examined all invasive tumors diagnosed in 1996, and identified any with reports of the same site that were diagnosed from 1979 to 1995. The reports were classified in one of three ways: (1) the traditional New York rules (one tumor per site per person per lifetime), (2) modified SEER primary rules where judgment at the central registry level was used, and (3) strict computer application of the SEER primary rules. The three rates then were compared. Adaptation of the modified SEER rules
increased the multiple primary coding by 8.3 percent and was found to be beneficial in terms of case completeness.

For 1996, the registry had 130,600 reports on 88,000 tumors. Approximately 62 percent of all tumors had only one report, leaving 38 percent with more than one report. Sixty-four percent of the reports agreed on the date of diagnosis. For 19 percent, there were incomplete dates. An example was presented to highlight the difficulties faced by registries when trying to apply multiple primary rules. One woman with multiple tumors had six New York State hospital reports and one out-of-state report. The diagnosis dates did not correspond to the hospital admission dates. The patient had three breast cancers and an endometrial cancer, but discrepancies across the reports made it difficult to determine how many cancers the patient had. The New York State Cancer Registry receives approximately 50 percent of its reports from facilities that do not have an approved cancer program of the American College of Surgeons (ACoS).

When using the modified SEER rules, the registry drops the 2-month diagnosis rule because it feels it is impractical to implement, particularly because of unreliable information on the date of diagnosis. Many of the nonspecific site codes are not optimally grouped or addressed in either SEER or IARC multiple primary rules. For example, base of tongue (C01) and other unspecified parts of the mouth (C06.9) are considered distinct sites.

In addition, the entire C49 category (soft and connective tissue) is problematic, because rules based on a site rubric ignore these tumors. For example, one report might reference soft tissue of the abdomen and another could reference uterine sarcoma; these could be the same cancer. Metastatic site codes also are somewhat of a problem, specifically any tumor that is coded to retroperitoneum or peritoneum is considered suspect by the New York State Cancer Registry, because they are common metastatic sites.

It is very difficult to implement SEER rules at the central registry level where access to the medical record is limited, and registries have insufficient resources to follow back on all cancers. The method used for ascertaining multiple primary cancers has a significant effect on rates. The effect varies by site, and is most pronounced for breast and colorectal cancers. Accurate SEER primary ascertainment requires more personnel time and expertise than implementing the IARC rules.

Discussion

It was noted that cancer registries do not have enough staff to conduct followback on every patient, and that registrars sometimes must rely on their judgment to code cases. When examining multiple primary cancers, registrars should consider stage and treatment, in addition to primary site and histology (convincing reporting facilities to report site and histology text has been an ongoing struggle). Dr. Schymura noted that the New York State Cancer Registry receives approximately 500,000 notifications every year, many of which must be linked to registered cases, often leading to a multiplicity of diagnoses for the same case. When following back on representative samples, New York State Cancer Registry staff find that fundamental errors from single notifications coming into the registry often are the most problematic.
For registrars, determining how many lesions a patient has is a bigger problem than applying the SEER rules (there often are many reports on the same lesion). The SEER rules cannot be applied to five separate reports for the same patient, because the rules assume that there are five separate lesions even though this may not be the case. Dr. Schymura noted that it is extremely difficult to know what to do at the central registry level when information is limited and when only 50 percent of cases originate from Commission on Cancer (CoC)-approved programs.

NCI Initiatives on Multiple Primary Cancers
Ben Hankey

Several NCI initiatives on multiple primary cancers were presented. The NCI is developing a monograph on multiple primaries. This effort involves representatives from NCI’s Division of Cancer Epidemiology and Genetics (DCEG) and the Division of Cancer Control and Population Sciences (DCCPS). The monograph will be a follow-up to the Connecticut/Denmark multiple primary monograph described by Dr. Young. The DCEG is taking the lead for most chapters, and the DCCPS is coauthoring. Work on the monograph began a few years ago, and most chapters have been completed. It is anticipated that the monograph will be submitted for publication in approximately 1 year.

The National Institute on Aging has released a Program Announcement for research on cancer and aging that includes statistical methods as well as any and all aspects related to the impact of multiple primary cancers. Research and etiology on multiple primary cancers has been part of important discussions, with great interest and opportunities for research on survivorship. Multiple primary data are being used to model methods for estimating the proportion of patients who are cured of cancer as well as adjusted rates of survival for second cancer occurrence/recurrence.

Panel Discussion—Issues in Data Collection and Data Quality

Four panelists, Frances Ross, John Young, Carol Scott-Connor, and Lynn Ries, conducted a discussion of issues related to data collection and data quality.

How simple or complex must the definition of multiple primaries be to produce useful information? In many cases, the definition is going to be site-specific. The definition is more problematic for registries than for physicians. In looking at the SEER Program Code Manual, Third Edition’s six rules for multiple primaries, Rule 5, which addresses paired organs, is where most of the problems are encountered. Perhaps the rules should be rewritten; more is understood about the biology of cancer now than when the rules were written. With the use of ICD-O-3, and more extensive use of combination codes, registries may see an artificial drop in the incidence of the disease because conditions that would previously have been counted as two cancers now will be counted as one cancer. SEER is planning to convene an expert panel to examine ways to better define and code histology, the current rules are very complicated. However, if individual site-specific rules are adopted, it will be more complex, make registries less efficient and more costly, and will increase difficulty for pathologists. However, abstractors would welcome clearer, more specific rules.
What are the resource requirements to collect useful data? The information has to be in the medical chart, and the abstractors and coders must be well trained to identify appropriate cases and code the information. The more complex the process becomes, the more training and resources will be needed. A national shortage of certified tumor registrars exists, and registries are relying on fewer appropriately trained and more uncertified individuals for case ascertainment and coding information. Accurately classifying and coding multiple primaries requires years of experience, given the complexity and lack of specificity of the SEER rules.

Is it realistic to presume that resources will be available to maintain a high level of accuracy in the collection of multiple primary cancer data? In many cases, resources are not adequate for registries to perform their current duties, and resources may vary from registry to registry. Recommendations to improve multiple primary coding likely will result in more work for registries. For example, if the 2-month rule is dropped, registries will get many more reports than they do at present, so there will be more case reports to consolidate and resolve. Cases that have to be merged and consolidated from multiple reports significantly drain a registry’s resources. Registries in the east, where there is a larger population, rely much more heavily on the ACoS-affiliated registrars, but in the west and in some of the sparsely populated states, there are few ACoS hospitals, and the work falls more heavily on the registries to make coding decisions regarding multiple primaries. It may be helpful to flag the reporting form to indicate cases of multifocal or multicentric tumors, etc. Depending on how the rules for multiple primaries change, the resources available to cancer registries may have to change as well.

The IARC rules are simpler than the SEER rules; perhaps, they could be modified slightly to more effectively address sites such as breast, where the IARC rules undercount primaries that are important from a clinical perspective. In the future, interest will likely increase in determining why one breast cancer patient has multicentric disease as opposed to another who has multiple breast tumors. Synchronous tumor information will become more valuable as treatment becomes more individualized. Is multicentricity in the breast different than multicentricity in the lung or in the colon? With the current set of rules, registries are missing more multicentric cancers in the lung than in the breast. One approach to resolving this may be to create an indicator variable that would allow registries to follow back for further information as part of special studies. Flagging cases for future study of multicentric or multifocal disease could be a cost-effective approach.

What are the ongoing continuing education requirements to maintain a high level of accuracy in the collection of multiple primary cancer data? Education and communication between registrars and the data collectors, abstractors, and physicians must be improved so that all are aware of uses of the data and the importance of following coding rules precisely and completely documenting all relevant information in the medical record. Interactive, accessible, and current information on survival rates for very specific clinical presentations would be useful to clinicians to respond to patient concerns and queries. As an example, Dr. Edge briefly presented a Web-based program, called Adjuvant!, that uses data from a research group in San Antonio to illustrate the benefits of therapy for breast cancer based on age, comorbidity, estrogen receptor status, grade, size, lymph node status, and type of treatment. The Internet also may be a viable option for offering physicians continuing education credits by including information about cancer, multiple primaries and other etiologic, epidemiologic, and clinical factors that would be incorporated into an Internet resource.
Training on multiple primaries is not consistent, and in some cases, not accurate. Furthermore, few individuals are qualified to provide this training. Despite the high level of consistency with how things are done within a registry, registries vary widely in how they apply rules. Therefore, another educational challenge is training registry employees to apply multiple primary rules reliably and consistently across registries. One possibility is to create a Web-based resource for registrars that promotes standardization after the multiple primary rules are refined and clarified.

How can we obtain highly reliable, useful, and valid data from the highly decentralized cancer surveillance system in existence in the United States today? Cancer patients typically are not diagnosed, treated, and followed up at a single facility. It is difficult to capture all of this information and examine the sequence from biopsy to treatment, particularly when registries are obtaining different types of information from different sources. It is hoped that as processes become more electronic, this will become less burdensome. Data on chemotherapy typically are incomplete, as are data for radiation therapy, because they often occur outside the cancer registration infrastructure, so registries are missing information about some parts of treatment regimens for some cancers. Using edit flags may help. Another problem is the mobility of the population, including cancer patients, who may live in one state for part of a year, and another state for the remainder of the year. No system exists for tracking in- or out-migration as people move from state to state. This impacts the accuracy of incidence reporting as well as survival statistics, and in general, describing disease burden accurately.

Participants were asked to complete a “homework” assignment in which they were instructed to determine how to code the number of cancers in a series of 10 patients. Results of the exercise (participants had widely varying answers to many of the cases) highlighted the difficulties facing cancer registry staff when limited, conflicting, or confusing information appears on medical records.

Section III: Uses of Multiple Primary Data

Cohort and Case-Control Studies of Second Primary Cancers
Lois B. Travis

The 5-year survival rate of patients with cancer at all sites, ages, races, and genders increased significantly from the 1930s (25%) to the early 1990s (59%). The acute toxicity of cancer therapy has been well characterized, and includes nausea/vomiting, myelosuppression, and others. Relatively recently, more has been understood about late effects, such as second cancers or renal damage. Radiation and chemotherapy can induce second cancers, and numerous other factors can promote the development of second cancers, such as lifestyle factors (tobacco, alcohol, diet, other); environmental factors (contaminants, occupation); host factors (genetics, immune function, hormonal); and other influences, such as gene-environment interactions.

Cancer registry data have been used to study multiple primary cancers in cohort studies for site-specific risk and temporal patterns as well as case-control studies examining the relationship of second cancers to antecedent treatment, delineation of dose-response relationships, and evaluation of latency patterns and other risk factors. The clinical and scientific importance of second cancers includes the opportunity to study carcinogenesis in terms of measured amounts of carcinogens, delineation of dose-response relationships, evaluation of latency and age, large
relative risks, and interactions. A series of studies on leukemia following platinum-based chemotherapy was discussed. This treatment was the cornerstone for treatment of ovarian and testicular cancers for three decades, but it was found to be associated with late carcinogenic effects.

The Leukemia Following Ovarian Cancer Study included data on 32,251 1-year survivors from SEER and the Connecticut Tumor Registry (before it became part of SEER). A total of 111 leukemias occurred in this cohort, with a significantly increased incidence of about fourfold. For those patients who were designated on their files as having received chemotherapy, the risk increased by 25-fold in 1–9 years after chemotherapy. The Leukemia Following Testicular Cancer International Study included 28,843 1-year testicular cancer survivors from the SEER Program and Connecticut Tumor Registry as well as Sweden, Denmark, Finland, and Ontario. A total of 64 leukemias occurred in the cohort. Patients who had chemotherapy were found to have 12- to 15-fold increased risks of developing leukemia. [Source: Travis LB, Gospodarowicz M, Curtis RE, et al J Natl Cancer Inst 92:1165-1171, 2000.]

To follow up these observations, two nested case-control studies were conducted. Results for ovarian cancer indicated that there was a fourfold increased risk of leukemia associated with platinum-based chemotherapy. The risk increased with increased cumulative chemotherapy dose, duration, and latency. The risk also increased significantly when cisplatin and carboplatinum analogues were used together versus separately. The results for testicular cancer were similar, with an absolute risk (650 mg cisplatin) of 16 excess leukemias per 1,000 testicular cancer patients. In short, these studies established the dose-dependent risk of leukemia after platinum-based chemotherapy. [Source: Travis LB, Curtis RE, Boice JD, et al. Cancer Res 56:1564-1570, 1996.]

It has been well established that a number of cytotoxic drugs can cause leukemia. One of the most important questions facing second cancer researchers is whether chemotherapy also can induce solid tumors. In an international study examining lung cancer incidence following treatment for Hodgkin’s disease that enrolled 19,046 patients, second lung cancers were found in 222 patients at an average latency of 10.8 years. All but 16 of these patients were in clinical remission from their Hodgkin’s disease. Data were collected on chemotherapy, radiation, and tobacco use. The risk of developing lung cancer increased significantly with increased number of cycles of alkylating agents and cumulative dose of chemotherapy and/or radiation. The risk decreased significantly with increased time since last treatment with alkylating agents. The data also indicated that there was a multiplicative (not an additive) association between smoking and treatment (alkylating agents and radiation). The clinical implications of this study are that: (1) the cumulative doses of radiotherapy and alkylating agents should be minimized; (2) smoking cessation programs are especially needed in this population; and (3) systematic, long-term follow-up of survivors in this population is warranted. [Source: Travis LB, Gospodarowicz M, Curtis RE, et al. J Natl Cancer Inst 94:182-192, 2002.]
Discussion

It was noted that when conducting these case-controlled studies, second tumor information, including treatment of the second tumor, is critical for selecting the cases. To obtain a large cohort of these types of patients, tens of millions of person years must be canvassed to yield an adequate number of cancer years, resulting in a predilection to using cases from long-standing cancer registries. Collaborating with cancer registries for these studies is ideal because the registries already have conducted the follow-up with patients and have identified the second cancers.

One participant asked whether selecting controls who have the same survival rate as cases but who have the potential to become cases in the future results is an underestimation of risk. Dr. Travis did not believe this was the case, because she and her colleagues always have matched on latency. If a patient has been treated for testicular cancer, subsequently developed leukemia, but lived for 10 years because of the cancer treatment, that is more useful information than information from a testicular cancer patient who has lived for 3 years post-treatment and may still be at risk for developing leukemia. Dr. Travis noted that she and her colleagues are developing a study on stomach and pancreas cancers following treatment for Hodgkin’s disease. Despite the underreporting of chemotherapy administration, researchers are still able to use this information.

Surveillance Research and Multiple Primaries: Issues in Data Quality and Analysis
Betsy Kohler

During the past 3 years, two special NAACCR research groups on breast and ovarian cancers were convened among NAACCR members to conduct research and surveillance analyses, including several on multiple primaries. The NAACCR Analytic Files have been cross-sectional data files spanning 5 or 6 years. Although they can include 3 million or more cases, they are of limited value for multiple primary analyses. Beginning in 2003, however, the file will become a cumulative file with data beginning with a 1995 base year. The NAACCR Analytic File only includes data from high-quality cancer registries that have passed the NAACCR certification standards. In addition, registries also need to give consent for their data to be used in specific studies.

The frequency of multiple primaries on the NAACCR 1994–1998 Analytic File was examined with (in order) colorectal, breast, lung, prostate, bladder, and NHL being the most common sites for multiple primaries (based on a sequence number greater than 0). Cancers with the highest relative proportion of multiple primaries (compared to the number of single primaries in the same site) were, in order colon, bladder, kidney, melanoma, lung, and breast. These frequencies were, of course, affected by the maturity of the registries included, newer registries being less likely to have multiple primary tumors registered for patients.

In 2002, using the 1994–1998 NAACCR file, one study compared breast cancer rates computed after following both the SEER and IARC rules for defining a multiple primary. A 2.3 percent difference was found in the breast cancer rates during the 5-year interval, with SEER rules producing the higher rate.
In two other studies, multiple primary reports were reviewed for data quality. Assignment of the correct sequence number was the most common error in both an ovarian and a breast multiple primary study. Other inconsistencies between the two records included ethnicity, race, and unknown sequence number. These data problems came from otherwise high-quality registries, and perhaps should be considered as sentinel of the degradation of data quality on multiple primaries relative to indicators measuring more general aspects of quality cancer operations and registration. [Source: Howe HL, Weinstein R, Hotes J, Kohler, Roffers SD, Goodman MT. Multiple primary cancers of the ovary in the United States, 1992-1997. Cancer May 15, 2003;97/10(Suppl):2660-2675.

Discussion

Ms. Kohler agreed with participants that the rank frequency of multiple primaries on the NAACCR Analytic File was surprising, and many participants felt that the results may not be correct. Ms. Kohler clarified that the data included either the first or the second primary, and that more of the second of two or more primaries were included in the data. She also reminded participants that the data are preliminary and cover only a 5-year interval. Other participants felt that given that the participating registries were high-quality, these data could be viewed as a “wake-up call” for all registries.

A clinical perspective of the data presented was that definitions of “tubular carcinoma” and “infiltrating ductal carcinoma,” two diagnoses that clinicians consider to be the same histologic type, were considered different histologies, thus leading to an over-count of multiple primaries. Definitions and current registration rules that differ from clinical definitions also raised concerns about the information on synchronous tumors. The information on metachronous tumors, although from a truncated interval, is more likely to be consistent with clinical definitions.

This analysis may demonstrate the interpretation problems that can arise when registry data are used for research and are not of sufficient quality to address the study question. One approach may be to use data from registries that meet higher standards than even the gold standard registries (a participant explained that the gold standard only measures quality in producing accurate incidence rates for standard population groups and geographic areas). Another approach may be to send data back to registries with an explanation of what is wrong with the data and ask the registries to clean the data up and resubmit them. Even if the data are of very high quality, many inherent problems are associated with examining multiple primary data (e.g., short follow-up period).

Participants discussed the value of inter-record edits in using registry data for studies of multiple primaries. Although inter-record edit programs are available, many registries are not routinely using them to identify errors and inconsistencies among multiple records for the same tumor. In 2003, NAACCR will begin to require that inter-record edits be run on data in their annual Call for Data. A strong need for starting a cumulative file for conducting these types of analyses exists.
Analysis of multiple primary data is affected by the number of years of data that are available. Results from studies that include only short intervals may be different than those that have long-term survival and follow-up information, a point demonstrated in Dr. Lynn Ries’ presentation, which follows.

**Surveillance Research in SEER**

**Lynn Ries**

In examining the distribution of sequence number by age in SEER data, about 90 percent of those in the under 50 age group have only one primary. However, by age 75, 25 percent of cancers are multiple cancers. As the population ages, there will be more cases of multiple primary cancers (there will be fewer multiples with prostate because there cannot be prostate-prostate cancers as there can be breast-breast cancers). Melanoma has the highest proportion of most second primaries, followed by colorectal cancers. The length of time a registry has been in existence determines what a registry’s sequence numbers will be (sequence numbers should last over the life of a patient). Registries that started recently will have fewer second primaries than more mature registries, but the pattern will stabilize once a registry is about 15 years old.

Overall, based on SEER data, approximately 13.2 percent of invasive cancer at all sites are second primary cancers. A larger proportion of breast cancers are first primaries rather than second primaries, and larger proportions of prostate and colorectal cancers are second primaries rather than first primaries.

In examining the difference between the SEER rules and the IARC rules, an analysis of 2,000 diagnoses with the SEER and IARC standards applied to them found a 6 percent higher incidence of multiple primary breast cancers using the SEER rules. Similarly, a 3.7 percent higher incidence of colorectal cancers was found using the SEER rules versus the IARC rules. According to SEER rules, coders can choose the worst of two cancers diagnosed at the same time and sequence that cancer first. IARC rules instruct coders to choose a random tumor instead. IARC is considering adding sequence number, but they are concerned about adding extra fields that some registries may not collect.

Survival analyses are affected by the multiple primary definition and are complicated by the number of multiple primaries. An analysis of lung cancer survival using SEER data found an overall 5-year relative survival rate of 13.2 percent. Patients with one and only one cancer (their lung cancer) had a 5-year survival rate of 12 percent. If patients had another primary after the lung cancer, the 5-year relative survival rate for the lung cancer was 53 percent. However, 79 percent of the lung cancer cases had only one primary tumor. Interpretation of these statistics can be difficult because one must take into consideration that a patient had to live long enough to be diagnosed with a second primary. Thus survival by sequence number is a conditional probability: sufficiently long survival after the first primary. When lung was the first cancer, the 5-year survival rate was 3 percent, while it was 15.7 percent when lung was the second cancer.

A multiple primary system will be available in SEER*Stat in approximately 1 year; it will be presented as a separate module. The system calculates the number of observed new primaries expected among the cancer patient cohort over a specific amount of time.
Discussion

It was noted that melanoma was the cancer type most associated with second primaries in the SEER data, followed by colorectal cancer. The data item, sequence-number-central, is used even though in registries’ early years, some patients had as their first sequence number, a sequence number of two because the first cancer pre-dated the reference date of the registry. These cases are kept because it is not known whether the cancer on file is the same as the cancer not on file. It is assumed that the person had a first malignant cancer, so it is left in the database as a second primary.

Working Group Discussion II

Participants were asked to discuss and answer a number of key questions related to uses of multiple primary data. The working group responses appear in Table 2.

Table 2. Working group responses to questions on the uses of multiple primary data.

<table>
<thead>
<tr>
<th>What is your group’s definition of multiple primary?</th>
<th>Etiology</th>
<th>Epidemiology/Surveillance</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metachronous tumors are more important than synchronous tumors.</td>
<td>Something biologically and clinically meaningful that is easy to operationalize.</td>
<td>Two or more distinct tumors in the same organ, opposite side of paired organs, or different organs, regardless of time (site-specific issues need to be addressed, clinical input is needed).</td>
<td></td>
</tr>
<tr>
<td>Only use subsequent tumors if it is more than 1 year from first diagnosis of cancer.</td>
<td>Use for multiple statistical measures: incidence, prevalence, survival, risk, probability of developing cancer, burden on health care system.</td>
<td></td>
<td></td>
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<tr>
<td>Current rules work well most of the time—the focus should be on simultaneous tumors in the same site and examining specific troublesome sites.</td>
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<table>
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<tr>
<th>What were the high points of your discussion?</th>
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<tbody>
<tr>
<td>The ability to measure the burden of disease must remain in light of any new recommendations. The impact of any changes on incidence rates should be evaluated. Any changes should simplify and clarify the workload for registries because quality will be improved and resources to do this will not increase.</td>
<td>Perhaps the synchronicity term could be modified to extend potentially to 1 year. This would help in some of the counting issues.</td>
<td>Site specificity.</td>
</tr>
<tr>
<td>Multiple primary rules should be reviewed. Are they consistent with the biology of the tumors by site? Are site-specific rules needed?</td>
<td>It would be helpful to add the multiplicity designations with five categories: multifocal, multicentric, don’t know, single lesion, and mixed multifocal-multicentric.</td>
<td>Therapy decisions are not based on registry data.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The registry data are important for surveillance and as a base for clinical research.</td>
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<table>
<thead>
<tr>
<th>Are you using the data on multiple primaries that are being collected?</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Mostly on metachronous tumors, and mostly just site, diagnosis date, and histology (not stage or treatment of second cancers).</td>
<td>Yes, and more are needed.</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>Perhaps there also should be some site-specific rules.</td>
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</tr>
<tr>
<td><strong>Do you modify the definitions or rules to do your work?</strong></td>
<td><strong>Etiology</strong></td>
<td><strong>Epidemiology/Surveillance</strong></td>
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<tr>
<td>Should have a flow chart/business modeling to determine the number of primaries. Simplify the rules. Reduce the amount of data that need to be collected on subsequent tumors. Consider reporting incidence for first cancer (only one per person, as for mortality and survival), or report incidence for first cancer only for each site/type?</td>
<td>Yes, for resequencing, counting differently for specific purposes, and correcting codes.</td>
<td>Clinicians do not use the rules.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Is there information that is collected that is not used?</strong></th>
<th><strong>Etiology</strong></th>
<th><strong>Epidemiology/Surveillance</strong></th>
<th><strong>Clinical</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is stage or treatment of second, third, etc., cancers ever studied? Can many of the data variables on subsequent tumors be dropped, but keep the fact of acknowledge them (by sequencing them) for consistent incidence rates? Are multiple tumors (e.g., breast) being collected when clinicians do not even think of them as separate tumors? Information on synchronous tumors is used to calculate rates. Patient-linked information is not used as often.</td>
<td></td>
<td>Yes. Databases are being designed backwards (they are being built and then research questions are being asked, instead of asking research questions and building databases based on these questions).</td>
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<table>
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<tr>
<th><strong>Do you need other data?</strong></th>
<th><strong>Etiology</strong></th>
<th><strong>Epidemiology/Surveillance</strong></th>
<th><strong>Clinical</strong></th>
</tr>
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<tbody>
<tr>
<td>The number of reportable tumors per person. What items would the recommended multiplicity indicator include? A possible application for using synchronous tumors in research is to answer questions related to family syndromes or environmental factors. A multiplicity indicator needs to be defined. Use data to establish cutpoints (e.g., 4 months, 1 year, etc.) for defining synchronous and metachronous timing intervals. Clinician input/assistance is needed for some decisions.</td>
<td>Site-specific multiple primary data. Identify problem/common multiple primary sites. Form multidisciplinary task force(s) focusing on disease sites, consider collaborations with groups already forming disease site task forces (ACoS, ASCO). Problematic multiple primary sites include breast, bladder, melanomas, colon, oral cavity and pharynx, head and neck.</td>
<td></td>
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</table>
Do you need other data?

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</tr>
</thead>
<tbody>
<tr>
<td>The number of reportable tumors per person.</td>
<td>A multiplicity indicator needs to be defined.</td>
<td>Site-specific multiple primary data.</td>
</tr>
<tr>
<td>What items would the recommended multiplicity indicator include?</td>
<td>Use data to establish cutoff points (e.g., 4 months, 1 year, etc.) for defining synchronous and metachronous timing intervals.</td>
<td>Identify problem/common multiple primary sites.</td>
</tr>
<tr>
<td>Possible application for using synchronous tumors in research: answer questions related to family syndromes or environmental factors.</td>
<td>Clinician input/assistance needed for some decisions.</td>
<td>Form multidisciplinary task force(s) focusing on disease sites, consider collaborations with groups already forming disease site task forces (ACoS, ASCO).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Problematic multiple primary sites include breast, bladder, melanomas, colon, oral cavity and pharynx, head and neck.</td>
</tr>
</tbody>
</table>

A suggestion for defining multiple primary cancers for clinical purposes is to start with SEER as the base, but include site-specific definitions of multiple primaries, particularly as they relate to multiple primaries in the same organ. Defining multiple primaries in different organs is a matter of determining metastatic disease versus primary cancer. The clinical significance of a multiple primary cancer affects the recommendation for treatment and patient management. Developing edit checks around the issue of multiple primary cancers was recommended, as was developing a flow chart for the processes associated with coding multiple primaries. This has been tried and is complicated. The use of Unified Modeling Language (UML) would be helpful and may point out some deficiencies that have not yet been noticed. It also may help guide prioritization of coding rules. Expertise in UML diagrams or other flow chart or modeling could improve its feasibility.

Most of the concern with multiple primaries is with synchronous tumors, especially in the same organ. Is it worthwhile to spend a great deal of time trying to identify multiple lesions in the same organ and determining their clinical significance? It might be more effective to go back at a later date and obtain the pathology report instead of spending time trying to obtain the information up front. Should only one tumor per organ be collected, or does every single tumor need to be collected? The answer hinges on the definition of the term “organ.” Should only one synchronous tumor be counted per organ? It may make sense to report the number of tumors as well as the number of people with tumors. To date, there has been a good deal of interest in the treatment and the staging with regard to first primary cancers, but less interest in studies of staging and treatment received for the second, third, and fourth primaries is evident. However, all primaries are included in incidence statistics and all this information is necessary in reporting the survival statistics.
Recommendations/Additional Comments

After the discussion of the working group questions presented in Table 2, workshop participants made the following recommendations/additional comments:

• This group would like to see SEER take the lead in reviewing their rules for determining multiple primaries. The current rules should be re-examined in light of the known biology of the disease, while maintaining comparability with historical data.

• One of the first steps should be to determine the prioritization of rules and develop a flow chart that maps out the decision making process for coding multiple primaries and prioritizing the coding rules. Site-specific experts and histology experts will need to be included in this process. In defining the new rules for multiple primaries, mapping data collection and forward-backward compatibility should be considered. Part of the problem in developing the flow chart will be prioritizing the decisions. An initial step should be writing a rule that allows for mapping with prioritization. Then, the flowchart can be developed and submitted to site-specific groups, which will lead to more uniform productivity. One goal of the flowchart should be that when followed by users, they would consistently come to the same decision or result. Another goal is simplification and streamlining the process. This flow chart, if it can be developed, could serve as a jumping off point for a multidisciplinary task force charged with addressing multiple primary issues.

• Smaller, site-specific task forces should be used to focus on the site-specific multiple primary issues. A multidisciplinary task force should be formed to tackle many of these issues. Some organizations (ACoS and ASCO) have existing site task forces that could be tapped for expertise and guidance. The NCI is recognized as the standard-setting organization for defining multiple primary cancers. The NCI should take the lead in forming the multidisciplinary task force, and may contract with NAACCR, IMS, etc. to facilitate its implementation.

• Consider taking a stepped approach, tackling specific sites one at a time, possibly starting with breast, colon, and melanoma. Work first with the flowchart, prioritize rules, develop guidelines, and take them to an expert site-specific group. This group then can address multiple primary issues, concentrating mostly on synchronous primaries (e.g., primaries in the same breast for the breast group, and primaries within the same sub-site for the colon group). Within the breast, the big issue is synchronous tumors that are not necessarily separate and true unique primaries.

• The most problematic cases are multiple tumors that occur at the same time in the same organ (synchronous tumors).

• Defining a multiplicity indicator (a simple way to flag records without abstracting a second tumor) that is site-specific would be extremely helpful and would reduce registries’ workloads if rules for computing surveillance statistics (incidence) were also changed to include only one synchronous tumor of the same organ.
One central question is whether the definition of multiple primary cancers needs to be changed or modified. Perhaps synchronous tumors should be counted as one primary, with decisions as to how these should be abstracted. The rules for addressing these need to be better defined, most likely with the help of site-specific experts. The addition of a multiplicity indicator would be sufficient for special studies and etiologic research.

Historically, the decision has been made to collect more rather than less data. Some consideration should be given to either collecting less data or collapsing the data.

The political implications of any rule changes need to be carefully considered with regard to historical trends and descriptions of current cancer burden. However, since data were first collected in the U.S. in the 1930s, the definition of multiple primary cancers has evolved and been revised many times.

**Problems and Recommended Solutions for the SEER Multiple Primary Coding Rules**

Workshop participants discussed the six rules for determining multiple primary cancers as outlined in the *SEER Program Code Manual, Third Edition*. Rules or components of rules that are problematic or inaccurate were identified. It was suggested that this discussion could be valuable for any site-specific working groups that are developed to address multiple primary issues in greater detail. To begin with, some aspects of the *Manual’s* definitions of multiple primary cancers are not sufficiently clear or precise. The definitions appear as follows in the *SEER Program Code Manual, Third Edition*: 
Definitions:

1. **Site differences:**
   Main rule: Each category (first three characters) as delineated in ICD-O-2 is considered to be a separate site. There are two sets of exceptions to this rule:

   **EXCEPTION A: Certain specific sites.** For the following three-character categories, each subcategory (4 characters) as delineated in ICD-O-2 is considered to be a separate site.
   - Colon (C18)
   - Anus and anal canal (C21)
   - Bones, joints, and articular cartilage (C40–C41)
   - Melanoma of skin (C44)
   - Peripheral nerves and autonomic nervous system (C47)
   - Connective, subcutaneous and other soft tissues (C49)

   **Examples:**
   - Transverse colon (C18.4) and descending colon (C18.6) are considered separate sites.
   - Trigone of bladder (C67.0) and lateral wall of bladder (C67.2) are considered subsites of the bladder and would be treated as one site—either overlapping lesion of subsites of the bladder (C67.8) or bladder, NOS (C67.9).

   **EXCEPTION B: Certain sites that were combined in the first edition of ICD-O.** Between the first and second editions of ICD-O, some subcategories having code numbers with the same first three characters in the first edition of ICD-O were split into separate three-character categories in ICD-O-2, and some subcategories having code numbers with different first three characters were grouped under the same first three characters. To avoid artificial change in the number of cancers by site over time, the SEER Program groups the subcategories as they were grouped in ICD-O-1. The table on pages 9–10 shows these exceptions [NOTE: the table referenced above is not reproduced here; it can be found on pages 9–10 of the SEER Program Code Manual, Third Edition.]

   To use the table, locate the horizontal row containing the ICD-O-2 codes for each of a pair of subsites/subcategories that are being checked. If they are in the SAME horizontal row, consider them to be the SAME site, whether the first three characters are the same or different. If they are in DIFFERENT horizontal rows, consider them to be DIFFERENT sites, whether the first three characters are the same or different. If both are not on the table, refer to the Main Rule and Exception A above.

   Note that when determining multiple primaries using the table on pages 9–10, both invasive and in situ cancers are to be considered.

   **Examples:**
   - Base of tongue (C01.9) and border of tongue (C02.1) are considered subsites of the tongue and would be treated as one site and coded as C02.8, overlapping lesion of the tongue or C02.9, tongue, NOS.
   - An invasive transitional cell carcinoma of the renal pelvis (C65.9) and an in situ transitional cell carcinoma of the mid-ureter (C66.9) would be considered one site in the urinary system.

2. **Histologic type differences:** Differences in histologic type refer to differences in the FIRST THREE digits of the morphology code, except for lymphatic and hematopoietic diseases (for which see pages 14–37).

3. **Simultaneous/Synchronous:** Diagnosed within two months of each other.
Problems noted in the definitions section included the following:

- **Site differences.**
  
  – EXCEPTION A. What is the rationale for delineating each subsite as a separate site for the listed exceptions (colon, anus, bones, joints and cartilage, skin [if melanoma], peripheral nerves, autonomic nervous system, and connective and soft tissue)? Are these reasons still valid, and should each of these subsites continue to be regarded as separate sites? What about non-specific sites, such as C14.8 (overlapping lesion of lip, oral cavity and pharynx) or C39.9 (ill-defined sites within the respiratory system), should these be considered the “same site” as some other codes not in the same 3-character rubric?

  – EXCEPTION B. Should the practice of combining some 3-character categories and calling them the “same site” continue to remain consistent with IDC-O-1? For example, two tumors, one in the adrenal gland and one in the pituitary gland, would be considered “multiple lesions of the same site” by the current definition. Also, when multiple tumors exist in multiple sites that are considered the “same site” and a single primary is to be abstracted, there are no instructions as to how the topography code is to be assigned.

- **Histology differences.** Some specific problems were introduced with ICD-O-3. The new code 8046 (nonsmall cell carcinoma) is considered to be the same histology as 8041–8045 (small cell carcinomas) by this definition. Should it be considered the same as some specific carcinomas, such as 8012 (large cell carcinoma) or 8070 (squamous cell carcinoma)?

- **Synchronous diagnoses.** Is the 2-month rule arbitrary? Would 4 months (the interval used for collaborative stage) or even 1 year be more appropriate? Should the timeframe be site specific or based on treatment?

Participants also would like to see a chart or outline of the specific differences in the multiple primary table for the hematopoietic diseases that was in effect prior to 2001 versus the one in effect with 2001+ diagnoses and ICD-O-3 coding. They would like to know if the clinical understanding of these diseases has changed with regard to subsequent diagnoses being considered new primaries versus progression of the same disease.

The Minnesota Cancer Surveillance System has developed a table of same-site and same-histology pairs and has linked the nonspecific codes with the relevant codes, using a computer algorithm to flag reports that should be manually reviewed. This could be an important resource for reviewers.

Workshop participants then discussed each of the following six rules for determining multiple primary cancers:
1. **A single lesion of one histologic type is considered a single primary, even if the lesion crosses site boundaries.**

   *Examples:* A single lesion involving the tongue and floor of the mouth would be one primary.

   A single, large mucinous adenocarcinoma involving the sigmoid and descending colon segments is considered one primary.

Rule 1 is acceptable, as long as the definitions of site are addressed. The rule should be phrased so that coders who are new to these recommendations do not stop at Rule 1 if this cancer is a recurrence. The rule should specify that this is only one lesion. The IARC rules may have a suitable qualifier that can be used in this instance.

2. **A single lesion composed of multiple histologic types is to be considered as a single primary.** The most frequent combinations of histologic types are listed in ICD-O-2. For example, combination terms such as “adenosquamous carcinoma (8560/3)” or “small cell-large carcinoma (8045/3)” are included. Any single lesion containing mixed histologies is to be considered one primary.

   *Examples:* A single lesion containing both embryonal cell carcinoma and teratoma is one primary and would be coded to 9081/3, mixed embryonal carcinoma and teratoma.

   A single lesion of the liver composed of neuroendocrine carcinoma (8246/3) and hepatocellular carcinoma (8170/3) is one primary and would be coded to the higher ICD-O-2 code.

Rule 2 is acceptable.
3. If a new cancer of the same histology as an earlier one is diagnosed in the same site within two months, consider this to be the same primary cancer. If a new cancer of the same histology is diagnosed in the same site after two months, consider this new cancer a separate primary unless stated to be recurrent or metastatic.

**Examples:**

Infiltrating duct carcinoma of the UOQ right breast diagnosed March 1998 and treated with lumpectomy. Previously unidentified mass in LIQ right breast noted in July 1998 mammogram. This was removed and found to be infiltrating duct carcinoma. *Count and abstract as two primaries.*

Adenocarcinoma in adenomatous polyp in sigmoid colon removed by polypectomy in December 1998. At segmental resection in January 1999, an adenocarcinoma in a tubular adenoma adjacent to the previous polypectomy site was removed. *Count as one primary.*

EXCEPTION 1: Invasive adenocarcinomas of the prostate, site code C61.9, and invasive bladder cancers, site codes C67.0-67.9, with histology codes 8120-8130, are the exceptions to the above rule. For these cancers, a single abstract is required for the first invasive lesion only. If there is an in situ cancer followed by an invasive cancer, refer to Exception 2.

EXCEPTION 2: Effective with cases diagnosed January 1995 and after, if an in situ tumor is followed by an invasive cancer in the same site more than two months apart, report as two primaries even if stated to be a recurrence. The invasive primary should be reported with the date of the *invasive* diagnosis. (Note: The purpose of this guideline is to ensure that the case is counted as an incident case [i.e., invasive] when incidence data are analyzed.)

EXCEPTION 3: Kaposi’s sarcoma (9140/3) is reported only once and is coded to the site in which it arises. If Kaposi’s sarcoma arises in skin and another site simultaneously, code to skin (C44._). If no primary site is stated, code to skin (C44.9).

In earlier discussions, it was recommended to extend the 2-month interval to 4 months or 1 year. The effect of this recommendation may be to drop the incidence of second primary synchronous cancers, but the trends would be unaffected because earlier data could be recoded (i.e., tumors within 2–4 months would not be counted). Furthermore, it would only affect tumors in the same side of a paired organ or single organ (the timing is irrelevant for tumors in different organs). It was recommended that the six rules be reworded slightly so that a consistent nomenclature is used throughout (e.g., Rules 1 and 2 include a “single lesion;” Rule 3 includes a “new cancer”). The current nomenclature might lead individuals reading these rules for the first time to believe that “a single lesion” and “a new cancer” are two different things. The term “lesion” is used more frequently in subsequent rules.

There was some discussion of bringing back the multiplicity field for bladder and other sitespecific instances. Exception 2 is a problem because some bladder cancers are being double counted in incidence rates. A site-specific task force dealing with multiple bladder cancers should be charged with determining whether they should be reported only once, and no distinction should be made between *in situ* and invasive.
4. **Multiple lesions of the same histologic type**

   a. **Simultaneous multiple lesions of the same histologic type within the same site (i.e., multifocal tumors) will be considered a single primary.** Further, if one lesion has a behavior code of in situ and another a behavior code of malignant, still consider this to be a single primary whose behavior is malignant.

   **Examples:** At nephrectomy, two separate, distinct foci of renal cell carcinoma are found in the specimen in addition to the 3.5 cm primary renal cell carcinoma. *Count as one primary.*

   At mastectomy for removal of a 2 cm invasive ductal carcinoma, an additional 5 cm area of intraductal carcinoma was noted. *Count as one invasive primary.*

   b. **Multiple lesions of the same histologic type occurring in different sites are considered to be separate primaries unless stated to be metastatic.**

   **Examples:** During the workup for a squamous cell carcinoma of the vocal cord, a second squamous cell carcinoma is discovered in the tonsillar fossa. *Count as two primaries.*

   A patient with adenocarcinoma of the prostate undergoes a fine needle aspiration biopsy of a lung mass which is also adenocarcinoma. Special pathology stains indicate that the mass in the lung is a metastasis from the prostate. *Code as one primary of the prostate.*

This rule may need to be revised to reflect site-specific situations, particularly for breast. Rule 4 has problems due to the imprecise definition of “same site” and “same histology.” Changes in the definitions should eliminate the problem.
5. Multiple lesions of different histologic types

a. Multiple lesions of different histologic types within a single site are to be considered separate primaries whether occurring simultaneously or at different times.

Examples: A patient undergoes a right pneumonectomy for squamous cell carcinoma of the upper lobe. In the pathology specimen, an adenocarcinoma of the middle lobe is identified. Count as two primaries.

A patient undergoes a partial gastrectomy for adenocarcinoma of the body of the stomach. In the resected specimen, the pathologist finds both adenocarcinoma and nodular non-Hodgkin’s lymphoma. Count as two primaries.

Exception 1: For multiple lesions within a single site occurring within two months, if one lesion is stated to be carcinoma, NOS, adenocarcinoma, NOS, sarcoma, NOS, or melanoma, NOS and the second lesion is a more specific term, such as large cell carcinoma, mucinous adenocarcinoma, spindle cell carcinoma, or superficial spreading melanoma, consider this to be a single primary and code to the more specific term.

Exceptions for colon and rectum tumors:

i. When an adenocarcinoma (8140/_; in situ or invasive) arises in the same segment of the colon or rectum as an adenocarcinoma in a polyp (8210/_; 8261/_; 8263/_), code as adenocarcinoma (8140/_).

ii. When a carcinoma (8010/_; in situ or invasive) arises in the same segment of the colon or rectum as a carcinoma in a polyp (8210), code as carcinoma (8010/_).

Exception 2: Within each breast, combinations of ductal and lobular carcinoma occurring within two months of each other are to be considered a single primary and the histology coded according to ICD-O-2. These histologic combinations are ICD-O-2 morphology 8522/2 and 8522/3.

Example: A left mastectomy specimen yields lobular carcinoma in the upper inner quadrant and intraductal carcinoma in the lower inner quadrant. Code as one primary, C50.9 with morphology 8522/3.

Exception 3: Certain neoplasms may demonstrate both multiple foci of tumor and multiple histologic types that are commonly found together. In such cases, consult ICD-O-2 for a list of the most frequent histologic combinations. These multifocal, multi-histologic tumors occur most frequently in the thyroid, bladder, and breast. They are to be considered a single primary with a mixed histology.

Example: A thyroid specimen contains two separate carcinomas—one papillary and the other follicular. Code as one primary with morphology 8340/3, papillary and follicular.

b. Multiple lesions of different histologic types occurring in different sites are considered separate primaries whether occurring simultaneously or at different times.

Examples: In 1995, the patient had a mucin-producing carcinoma of the transverse colon. In 1999, the patient was diagnosed with an astrocytoma of the frontal lobe of the brain. Count as separate primaries.

During the workup for a transitional cell carcinoma of the bladder, the patient has a TURP which shows adenocarcinoma of the prostate. Count as separate primaries.
Rule 5a itself is sound, however, the problem is interpreting the meaning of “different histologic types,” particularly for breast. This could be complicated by the new combination codes in ICD-O-3. However, clinical input at the meeting indicated that many of the histologies listed as “different” are actually specific subtypes of ductal carcinoma. In terms of multifocal versus multicentric for the breast, the lesions should be counted as two primaries if they are more than 5 cm. apart (medically, the distance is more important than the histology). Multicentric cancers should be flagged. If in the first example in Rule 5a, one of the two tumors was “adenosquamous,” it would be unclear whether this example was one or two primaries. In Exception 1 to Rule 5a, the 2-month interval should be changed to be consistent with any revision to the definition of synchronous or simultaneous. Exception 2 needs to be updated for ICD-O-3 and the new combination codes. Some consideration should be given to removing breast from Exception 3 and combining Exception 3 with Exception 2. Rule 5b is acceptable as long as the definition of “different sites and histologic types” is clarified.

For Rule 6a, the opening phrase, “If only one histologic type is reported and,” should be deleted. For breast cancer, the rule should convey that each side of a paired organ should be considered separate organs, and tumors occurring in each are two separate primary cancers, with the exception of inflammatory breast cancer. Other sites may need exceptions as well. For Rule 6a, it may be easier to list site-specific rules rather than exceptions. Rule 6b will not apply to breast (whether or not the histologies are the same is irrelevant, if both sides of a paired organ are involved). Clinical experts for other paired organs should be consulted to determine if these rules (and exceptions) apply to other paired organs.
With regard to the rules for determining multiple primaries for lymphatic and hematopoietic diseases that follow the multiple primary rules in the *SEER Program Code Manual, Third Edition*, it was recommended that these rules be reviewed. New rules were implemented with ICD-O-3 and the justifications for any differences from ICD-O-2 should be provided. These rules currently disagree with the previous set of rules for these diseases as well as with the international rules for these diseases.

**Improving the Quality of the Reporting Data**

- The SEER multiple primary rules need to be reviewed, clarified, and possibly revised. A flow chart or decision diagram showing how to determine the number of primaries would be helpful.

- Consensus should be reached and a standard set of training materials should be developed. Pooling resources to develop one set of training materials, perhaps interactive Web-based training, may be one effective approach. Front-end data collectors should be given examples of the problems that registries encounter in trying to interpret and resolve multiple primary cases. When they are shown how the data are being used, it may serve as an incentive for them to more effectively collect and code the information. These individuals may be more receptive to changing their practices if they understand the rationale behind any changes.

- Additional edit checks should be created and implemented between first and later multiple primaries.

- It was recommended that all registries run an inter-record edits program to eliminate inconsistencies among tumors with regard to patient characteristics, sequence, and compliance to the multiple primary definitions and coding rules.

- A mechanism for states to provide feedback to their data providers would be helpful. Instructing coders to consider each side of a paired organ as a separate site will make application of the multiple primary rules much easier. If codes are applied in this way, it also will help data editors in consolidating records.

**Adjourn**

Before adjourning the workshop, Dr. Howe thanked attendees for their participation and thanked the NCI for its support.
References


