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Investigating Suspected Cancer Clusters and Responding to Community Concerns: Guidelines from CDC and the Council of State and Territorial Epidemiologists

Prepared by

Beth (Vivi) Abrams, MPH,¹ Henry Anderson, MD,² Carina Blackmore, DVM, PhD,³ Frank J. Bove, ScD,⁴ Suzanne K. Condon, MSM,⁵ Christie R. Ehemann, PhD,⁶ Jerald Fagliano, PhD,⁷ Lorena Barck Haynes,⁸ Lauren S. Lewis, MD,¹ Jennifer Major, MPH,⁸ Michael A. McGeehin, PhD,⁹ Erin Simms, MPH,¹⁰ Kanta Sircar, PhD,¹ John Soler, MPH,¹¹ Martha Stanbury, MSPH,¹² Sharon M. Watkins, PhD,³ Daniel Wartenberg, PhD¹³

1National Center for Environmental Health, CDC, Atlanta, Georgia; 2Wisconsin Department of Health Services, Madison, Wisconsin; 3Florida Department of Health, Tallahassee, Florida; 4Agency for Toxic Substances and Disease Registry, Atlanta, Georgia; 5Massachusetts Department of Public Health, Boston, Massachusetts; 6National Center for Chronic Disease Prevention and Health Promotion, CDC, Atlanta, Georgia; 7New Jersey Department of Health and Senior Services, Trenton, New Jersey; 8Haynes Ross Strategic, Seattle, Washington; 9Research Triangle Institute, North Carolina; 10Council of State and Territorial Epidemiologists, Atlanta, Georgia; 11Minnesota Department of Health, St. Paul, Minnesota; 12Michigan Department of Community Health, Lansing, Michigan; 13Robert Wood Johnson Medical School, Piscataway, New Jersey

The material in this report originated in the National Center for Environmental Health, Robin Ikeda, MD, Acting Director, and the Division of Environmental Hazards and Health Effects, Judith R. Qualters, PhD, Director.

Corresponding preparer: Kanta Sircar, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, CDC. Telephone: 770-488-3384; E-mail: ddq0@cdc.gov.

Summary

This report augments guidelines published in 1990 for investigating clusters of health events (CDC. Guidelines for investigating clusters of health events. MMWR 1990;39[No. RR-11]). The 1990 Guidelines considered any noninfectious disease cluster, injuries, birth defects, and previously unrecognized syndromes or illnesses. These new guidelines focus on cancer clusters. State and local health departments can use these guidelines to develop a systematic approach to responding to community concerns regarding cancer clusters. The guidelines are intended to apply to situations in which a health department responds to an inquiry about a suspected cancer cluster in a residential or community setting only. Occupational or medical treatment-related clusters are not included in this report. Since 1990, many improvements have occurred in data resources, investigative techniques, and analytic/statistical methods, and much has been learned from both large- and small-scale cancer cluster investigations. These improvements and lessons have informed these updated guidelines.

These guidelines utilize a four-step approach (initial response, assessment, major feasibility study, and etiologic investigation) as a tool for managing a reported cluster. Even if a cancer cluster is identified,

there is no guarantee that a common cause or an environmental contaminant will be implicated. Identification of a common cause or an implicated contaminant might be an expected outcome for the concerned community. Therefore, during all parts of an inquiry, responders should be transparent, communicate clearly, and explain their decisions to the community.

Introduction

In 1990, CDC published guidelines for investigating clusters of health events (the 1990 Guidelines) (1). The 1990 Guidelines did not focus on any specific disease and considered any noninfectious diseases, injuries, birth defects, and previously unrecognized syndromes or illnesses. Many state, local, and tribal health departments have used the 1990 Guidelines as a basis for developing and implementing protocols to investigate suspected cancer clusters, employing the four-step approach (initial response, assessment, major feasibility study, and etiologic investigation) identified in the 1990 Guidelines. Since the 1990 Guidelines were published, continued attention has been paid to suspected cancer clusters nationwide, leading CDC to publish additional details on the role of the guidelines in responding specifically to cancer clusters (2). Since 1990, many improvements have been made in the areas of data resources, investigative techniques, and analytic/statistical methods, and much has been learned from both large- and small-scale cancer cluster investigations.

This report augments the 1990 Guidelines by focusing specifically on cancer cluster investigations. The guidance provided in this report addresses additional subject areas that are deemed important by epidemiologists from state and local health departments (3). The additional subject areas include communications and resources for data and use of epidemiologic and spatial statistical methods. Useful websites, a resource not available in 1990, were added. The four-step process was retained, and more details were added.

Public health personnel in state and local health departments can use these guidelines to develop a systematic approach when responding to inquiries about suspected cancer clusters in residential or community settings. In addition, these guidelines might be helpful to a wider community of responders and epidemiologists who are concerned with such inquiries. These types of inquiries often are requested by community members or medical professionals concerned about what appears to be an unusually high number of diagnosed cases of cancer in a particular community, workplace, family, or school. Upon receiving an initial inquiry, health department personnel should respond rapidly to the caller's concerns, gather relevant information about the cancer cases, make a professional judgment on the likelihood that the reported situation could be an actual increase in cancer cases over those expected in a particular population, and determine whether further investigation is warranted. If appropriate, health department personnel then will need to provide resources for investigation of the suspected cluster, working with and involving members of the community as much as possible throughout the process.

Methods

In March 2010, the Council of State and Territorial Epidemiologists (CSTE) and CDC convened a workgroup (the authors of this report) to revise the 1990 Guidelines. The group comprised public health professionals selected by the leadership of CSTE's Environmental Epidemiology Subcommittee and by CDC's National Center for Environmental Health's (NCEH) Division of Environmental Hazards and Health Effects (EHHE). CSTE and CDC selected workgroup members with experience in responding to cancer cluster inquiries from communities and managing of cancer cluster investigations. Representatives included epidemiologists from state health departments who were selected in order to have input from states that represent a range of approaches to and capacities for cancer cluster investigations. In addition, CDC workgroup members included representatives from CDC organizations typically called upon to assist in cancer cluster investigations: NCEH/EHHE, the Agency for Toxic Substances and Disease Registry (ATSDR), and the National Center for Chronic Disease Prevention and Health Promotion's Division of Cancer Prevention and Control. CDC risk communications and statistical specialists, as well as epidemiologists at academic institutions experienced in cancer cluster investigations, participated in the workgroup.

The intent of the workgroup was to ensure a practical approach to the assessment, analysis, and investigation of response to cancer cluster concerns. Through regularly scheduled conference calls and meetings from March 2010 to May 2011, the workgroup identified areas that warranted change from the 1990 Guidelines and sources of new information to incorporate in the revision of the guidelines. For these topics, the medical librarians at the CDC Public Health Library and Information Center conducted a comprehensive review of the published, peer-reviewed literature. To identify articles related to community cancer clusters, librarians conducted a structured literature search using multiple databases including PubMed (National Library of Medicine, National Institute of Health, Bethesda, Maryland, available at <http://www.ncbi.nlm.nih.gov/PubMed>), MEDLINE (available at <http://www.nlm.nih.gov/bsd/pmresources.html>), and CAB (available at <http://cabdirect.org>). English language peer-reviewed articles published between 1969 and 2010 were searched by using the following medical subject heading (MeSH) terms: "cluster analysis," "cancer cluster," "neoplasm," "environmental illness," and "not occupational diseases." Through this process, 166 articles were identified. In addition, members of the workgroup recommended 26 publications, including publications on communications and statistical analysis as well as nonscientific publications related to cancer clusters, and three unpublished cancer cluster investigation reports that were relevant to topics addressed in the guidelines. All articles and reports were reviewed by the workgroup members. Regarding topics on which no new published evidence was available, expert opinion was sought from workgroup members. In October 2010, an in-person meeting of the workgroup was held to begin writing these guidelines.

In addition to convening a technical workgroup, CSTE sent a survey to all state and territorial epidemiologists to assess the needs of public health professionals when responding to cancer cluster concerns in order to direct the focus and content of the guidelines (3). The survey included questions about the most common activities which states engage in when addressing a cancer cluster inquiry and what type of information would be useful. This survey identified areas (e.g., communications, resources for data, and epidemiologic methods) in which more details would be useful. After discussion, review, and incorporation of the findings from the survey, the workgroup decided to retain and update the four-step approach first described in the 1990 Guidelines. Updates included incorporating new technological advances (e.g., use of the Internet and websites) for information on relevant data resources, statistical tests, and mapping techniques as well as lessons learned from recent cancer cluster investigations. One important update is the emphasis on the importance of developing a robust working relationship with the community as soon as possible, including clear two-way communication and transparency in all aspects of the response process, while maintaining scientific rigor.

The revised guidelines address questions about the availability of data, limitations associated with understanding cancer clusters, and decision-making about the extent to which inquiries can be followed up. For specificity, the revised guidelines are limited in scope to include only those situations in which a health department responds to an inquiry about a suspected cancer cluster in a residential or community setting. These guidelines do not address workplace cancer clusters or those related to medical treatment (e.g., cancers associated with pharmaceuticals). Workplace or occupational clusters and medically related clusters each present unique sets of circumstances, have unique and clearly defined populations at risk, and generally call for specific investigative methods, agencies, and partnerships (4,5). Similarly, these guidelines do not discuss diseases other than cancer that persons might suspect have occurred in clusters in their communities. However, some of the principles of risk communication, data analysis, and community involvement discussed in this report might be applicable to noncancer cluster investigations as well. Finally, the revised guidelines do not address routine surveillance conducted by cancer registries and programs to assess trends.

This report is divided into two sections and three appendices:

- The first section explains cancer cluster definitions, characteristics and lessons learned from recent investigations;
- The second section outlines a systematic, four-step process for evaluating potential cancer clusters;
- [Appendix A](#) provides an overview of sources of data and other resources useful for cancer cluster investigations;

- [Appendix B](#) describes considerations for developing effective communication strategies; and
- [Appendix C](#) highlights some useful statistical and epidemiologic approaches for investigating suspected cancer clusters.

Cancer Cluster Definitions, Characteristics, and Recent Investigations

Definition of a Cluster

CDC defines a cancer cluster as a greater than expected number of cancer cases that occurs within a group of people in a geographic area over a defined period of time (6). This definition can be broken down as follows:

- *a greater than expected number*: Whether the number of observed cases is greater than one typically would observe in a similar setting (e.g., in a cohort of a similar population size and within demographic characteristics) depends on a comparison with the incidence of cancer cases seen normally in the population at issue or in a similar community.
- *of cancer cases*: The cancer cases are all of the same type. In rare situations, multiple cancer types may be considered when a known exposure (e.g., radiation or a specific chemical) is linked to more than one cancer type or when more than one contaminant or exposure type has been identified.
- *that occurs within a group of people*: The population in which the cancer cases are occurring is defined by its demographic factors (e.g., race/ethnicity, age, and sex).
- *in a geographic area*: The geographic boundaries drawn for inclusion of cancer cases and for calculating the expected rate of cancer diagnoses from available data are defined carefully. It is possible to "create" or "obscure" a cluster inadvertently by selection of a specific area.
- *over a period of time*: The time period chosen for analysis will affect both the total cases observed and the calculation of the expected incidence of cancer in the population.

When a health agency is investigating a suspected cancer cluster, it can use these parameters to help determine whether the reported cancer cases represent an increase in the ratio of observed to expected cases. The health agency also can use the parameters to identify characteristics that indicate whether cases might be related to each other and to determine whether the cases warrant further investigation. In the sections that follow, guidelines are provided to outline how to make this determination, including the appropriate information to collect, the necessary deliberations, the factors to take into account, and the analyses to perform.

Characteristics of Cancer and Clusters

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) defines cancer as a term for a group of diseases in which abnormal cells divide without control and can invade nearby tissues (7). As a group, cancers are very common. Cancers are the second leading cause of death in the United States, exceeded only by diseases of the heart and circulatory system (8). One of every four deaths in the United States is attributable to some form of cancer. In 2009, approximately 1.47 million persons in the United States received a cancer diagnosis, and approximately 568,000 persons died from cancer (9).

Because cancer is common, cases might appear to occur with alarming frequency within a community even when the number of cases is within the expected rate for the population. As the U.S. population ages, and as cancer survival rates continue to improve, in any given community, many residents will have had some type of cancer, thus adding to the perception of an excess of cancer cases in a community. Multiple factors affect the likelihood of developing cancer, including age, genetic factors, and such lifestyle behaviors as diet and smoking. Also, a statistically significant excess of cancer cases can occur within a given population without a discernible cause and might be a chance occurrence (10,11).

Three considerations are important for suspected cancer cluster investigations. First, types of cancers vary in etiologies, predisposing factors, target organs, and rates of occurrence. Second, cancers often are caused by a combination of factors that interact in ways that are not fully understood. Finally, for the

majority of cancers, the long latency period (i.e., the time between exposure to a causal agent and the first appearance of symptoms and signs) complicates any attempt to associate cancers occurring at a given time in a community with local environmental contamination. Often decades intervene between the exposures that initiate and promote the cancer process and the development of clinically detectable disease (12).

Communicating effectively about the frequency and nature of cancer in explaining suspected cancer clusters can be difficult for public health agencies, and many of the scientific concepts involved (e.g., random fluctuation, statistical significance and latency period) might not be easy to explain to the community (13). Any number of community members, friends, or relatives with cancer is alarming and is too many from a personal perspective (11). When persons are affected personally by a case of cancer, they naturally seek an explanation of the cause of the cancer (13).

Cancer Cluster Investigations

As the 1990 Guidelines noted, finding a causal association between environmental contaminants and cancer is rare in a community cancer cluster setting (1). Evidence reported by state and local health agencies and federal agencies since 1990 that would suggest otherwise is limited, and most investigations of suspected cancer clusters do not lead to the identification of an associated environmental contaminant (10).

State and local health agencies receive approximately 1,000 inquiries per year regarding suspected cancer clusters (14). The majority of these inquiries can be resolved during the initial response, which consists of the initial contact and follow-up contact with the caller, if needed. The resulting health education can be an important public service (14). Even if inquiries concern events that meet the statistical criteria for a cancer cluster, investigations of suspected cancer clusters are unlikely to find an associated environmental contaminant (1,11). For example, one of the largest suspected cancer clusters investigated by CDC's NCEH and by other agencies concerned cases of childhood leukemia in Fallon, Nevada. Although initial analysis demonstrated a statistically significant ($p < 0.05$) increase in the number of cases, subsequent epidemiologic investigations did not identify a statistically significant association with environmental contaminants (15).

Suspected cancer clusters that consist of cases of one type of cancer, a rare type of cancer, or a type not identified usually in a certain demographic group are thought to be more likely to have a common cause (10). Even if these factors are present, the suspected cluster might not be associated with an environmental exposure and in fact might be a chance occurrence. A type of cancer under investigation might not be associated biologically with any environmental contaminants of concern in the community. In other words, a suspected environmental contaminant might not be in the causal pathway for a certain type of cancer. One common but false assumption held by persons not familiar with the scientific study of cancer is that a single environmental contaminant is likely to cause any or all kinds of cancer. Toxicologic and epidemiologic studies do not support this assumption. Cancer is not one disease, but rather many different diseases with different causal mechanisms (16).

In addition, two statistical issues influence the ability of the health agency to determine an association between the cancer(s) in question and environmental exposures. First, a suspected cancer cluster investigation with a small number of cases (e.g., one that involves a rare cancer type comprising only a few cases) might result in a lack of statistical power to detect an association. Second, because of the substantial number of cancer patients who might live in a community, a spurious association with an environmental contaminant can occur by chance alone, without the contaminant being a causal factor (17).

The health agency should avoid imprecise and post hoc definitions of such concepts as case, population, geographic area, or exposure period because such definitions might bias or limit an investigation. For example, case definitions that include different cancers generally are not useful, unless the environmental contaminant under consideration has been associated with multiple cancer types.

Latency and change of residence add to the complexity of these investigations. Because of the long latency period associated with cancers, behaviors and exposures that might have contributed to the development of cancer in a person typically occur years to decades before the diagnosis (e.g., malignant mesothelioma, a lung tumor, is associated with asbestos exposure). The latent period between first exposure to asbestos and death from mesothelioma is often 30 years or longer (18). Latency needs to be considered in an investigation of a suspected cancer cluster because it influences the exposure period relevant to the investigation. If a person with cancer did not live in the suspected cancer cluster area during the relevant exposure period (possibly 20 years previously), then that person's cancer cannot be related to an environmental contaminant of concern or to any exposure in the suspected cancer cluster area. Conversely, the latency period might limit the ability to detect a cancer cluster or identify cancers related to an environmental exposure that occurred in the past. In a mobile population, a cancer cluster resulting from an environmental contamination occurring years or even decades earlier might go undetected because exposed residents have moved away from the community before the cancer develops. Thus, as persons move in and out of different communities, their cumulative exposure profile will change.

Suspected childhood cancer cluster investigations have the same limitations as adult counterparts (19). However, because childhood cancers generally have shorter latency periods, changes of residence might be less of an issue in the investigation of suspected clusters involving childhood cancers (20). For example, in one California study of 380 children with a diagnosis of leukemia, approximately 65% of the study participants changed residence between birth and diagnosis (21), indicating that even among cancers with short latency periods, migration might be an important factor.

Because investigations rarely demonstrate a clear association with an environmental contaminant, investigations of community-based cancer clusters usually do not provide the resolution communities seek (11). Furthermore, a suspected cancer cluster investigation can have unintended consequences. An investigation can augment the existing fear and uncertainty in the community brought on by the perception that a suspected cancer cluster exists, which might have a negative social and economic impact (22). Therefore, during all stages of an inquiry or investigation, responders should not only be transparent and receive community input but also explain their decisions to the community.

Four-Step Process for Evaluating Suspected Clusters

Because major investigations require substantial resources and might not identify the cause of cancer cases, a stepwise approach is recommended. Both the likelihood of identifying a causal factor and the feasibility of studying the relationship should be considered before proceeding to the next step. Regardless of the extent of the investigational response, the process of responding to community concerns provides opportunities to increase communities' knowledge about cancer and to encourage participation in cancer screenings and healthy behaviors. For this reason, education and consultation are advised at all steps of the process.

Four steps are recommended to respond to a report of a suspected cancer cluster, including procedures, guidance on, and considerations for closing the inquiry or proceeding to the next step:

- [Step 1](#): Initial contact and response
- [Step 2](#): Assessment
- [Step 3](#): Determining the feasibility of conducting an epidemiologic study
- [Step 4](#): Conducting an epidemiologic study to assess the association between cancers and environmental causes.

These steps update the four-stage process discussed in the 1990 Guidelines but should be implemented with two qualifiers. First, the extent to which a health agency is able to follow these guidelines depends on existing resources and infrastructure. Second, the delineation between the steps is not necessarily fixed. Often, a health agency might choose to combine steps or to pursue a problem with several approaches. The four-step process is intended to be flexible, so that health agencies and their partners may use it as model guidelines and adapt it to their own existing protocols, resources, staffing, organizational systems, and policies.

Step 1. Initial Contact and Response

Description

The purpose of Step 1 is to collect information from the inquirer (i.e., the person calling, writing, or emailing the report of a suspected cancer cluster) so as to determine whether the inquirer's concern warrants further follow up. On the basis of the information collected, the health agency will need to decide whether to pursue the inquiry further. This step focuses on obtaining and evaluating whatever information the inquirer can provide as well as relevant data available to the health agency (e.g., data from cancer registry, census, and environmental databases [see [Appendix A](#)]).

The inquirer should be referred quickly to the responsible unit in the health agency, and the problem should not be dismissed prematurely (i.e., before information is collected). Although the majority of reports of potential clusters will be closed at the time of initial response because the inquirer's concerns are not consistent with a potential cancer cluster, the first encounter is often the health agency's best opportunity to educate the inquirer about the nature of cancer and suspected cancer clusters.

To be an effective initial responder and a successful manager of reports of a local suspected cancer cluster, the health agency needs to understand the context of the inquirer's concern, the nature of the perceived problem, the history of how it has or has not been reported to authorities, and if applicable how authorities have responded to date. In addition, other necessary background information should be gathered including demographic characteristics (e.g., age group) of the persons with cancer and the population group of which they are members. Not only is this information essential to the scientific investigation, but it is also important for effective information-gathering, communication and coordination with the inquirer or community. In addition, it is essential for the effective management of a suspected cancer cluster inquiry to be open, transparent, and thorough with respect to the evaluation of information and actions taken. It is also important to be sensitive and responsive to the inquirer's concerns.

Procedures

- The health agency responder (the responder) should be empathetic, listen to the inquirer's concerns, and record the information received.
- The responder should gather identifying information on the inquirer: name, address, telephone number, length of residence at current location, and organization affiliation, if any. However, the responder should comply with requests for anonymity and explain that the inability to follow up with the caller might hinder further investigation.
- The responder should gather initial data on the potential cluster from the inquirer: types of cancer and number of cases of each type, age of people with cancer, geographic area of concern, period over which cancers were diagnosed, and how the person reporting learned about the supposed cluster. Keep in mind that the inquirer might not know the true primary cancer diagnoses and will most likely not be aware of all cases of cancer in this area or during the period of concern.
- The responder should gather information from the inquirer about any specific environmental hazards or concerns, other risk factors (e.g., diet, infections, and family history) and other concerns in the affected area (e.g., the likely period of environmental contaminant exposures).
- On the basis of the information presented, the responder should make an initial judgment about the advisability of the health agency's pursuing an inquiry into the suspected cancer cluster. The decision might require discussions with other people in the health agency.
 - Multiple factors bear on this decision, but it is primarily based on whether the evidence as presented fits the definition of a cluster and the biologic plausibility that the cancers could share a common etiology. Such factors as reports involving a rare cancer or an atypical demographic distribution of a certain type of cancer (e.g., multiple cases of breast cancer in men) support the decision to investigate further and should be considered. If exposure to a specific environmental contaminant is a concern in the community, the consensus in the scientific literature regarding an association between the environmental contaminant and the cancer of concern should be considered.
 - Factors that do not support the need for further investigation include:

- cancer cases within family members who are linked genetically (especially cancers known to be strongly genetically related);
 - reported disease that might not be cancer;
 - different types of cancers not known to be related to one another;
 - a few cases of very common cancers (e.g., breast, lung);
 - cancer cases among persons who did not live in the same geographic location during the relevant timeframe based on latency, and thus could not have experienced a common carcinogenic exposure; and
 - the lack of a plausible environmental cause.
- The responder should clearly and accurately explain the rationale used to determine if an investigation will be pursued based on the information provided about the cases as well as the health agency's procedures. For example, the rationale for not pursuing an investigation could be that the reported cancers are unlikely to be related to plausible environmental exposure.
 - If an inquirer is reporting an event that is not a suspected cancer cluster but rather one involving a known or possible environmental contamination, the caller should be referred to the appropriate environmental resources agency. The responder should work with the health agency's communication experts to assess the potential community concern and impact, and prepare a plan to address concerns.
 - The health agency should provide responders with talking points about the nature of cancer, its frequency and occurrence, how different types of cancers reported are related to separate causes, that rates of disease do somewhat increase and decrease in a population over time (random fluctuations), and so forth. These points can be used to educate inquirers about cancer and to provide them with further resources that address their concerns.
 - If the information provided supports the decision to investigate the cancer concerns further, the health agency responder should notify the inquirer, explain what that entails and outline how the agency will follow-up with the inquirer and provide results. The responder should ask the inquirer if there are others in the community (e.g., other residents with this cancer type) who would like to have a report on the results of the next step.

Recommendations for Step 1

- The health agency responder should have expertise or training in cancer and/or environmental epidemiology.
- The responder should have training and experience in risk communication because, understandably, community residents can be extremely distressed by the perception of an excess amount of cancer in their community (22). The ability to make a judgment on the facts presented and to communicate the factors in that judgment clearly depends on having both scientific expertise and experience in communication.
- The responder should be knowledgeable about cancer, cancer prevention, and guidelines on investigating suspect cancer clusters. The responder also should be able to offer the inquirer easily accessible resources, such as the health agency's or CDC's cancer website (<http://www.cdc.gov/cancer>).
- If one person in the health agency with comprehensive expertise (i.e., in all areas described) is not available, the responder should collect initial information and tell the inquirer to expect a follow-up call. The responder should then discuss the case with colleagues who have the necessary expertise before responding to the caller with an initial judgment.
- The health agency and responder can access, at minimum, county-level cancer statistics from the state cancer registry to understand and explain the reported cases in an appropriate context. A list of state cancer registries is available at <http://www.cdc.gov/cancer/npcr>.
- If possible, the responder should be, or become, relatively familiar with the geographic area of concern, its demographic profile, and its history (e.g., industrial and residential development) in order to understand the health and environmental concerns of the community.

Decision to Close the Investigation at Step 1

A decision at Step 1 not to pursue an investigation is based on the determination that the reported cases

are unlikely to comprise a cancer cluster; therefore conducting a statistical assessment to determine whether an excess of cancer cases exists might be unsuccessful because the cancers are not likely to share a common, environmental etiology. This determination might involve multiple communications with the inquirer, as well as additional data-gathering. If the inquirer acknowledges and is satisfied with the decision not to move forward, the inquiry can be closed at this point. If the inquirer is not satisfied with the decision and the verbal explanation, then the health agency should consider providing a written explanation and include resources related to the decision. Regardless of the decision, the health agency should document in a permanent log all information about the inquiry and the decision.

Decision to Continue to Step 2

The data gathered at this point might suggest the need for further evaluation. If so, the health agency should elect to proceed to Step 2 to determine whether an excess of cancer cases exists.

Step 2. Assessment

Description

The primary purpose of Step 2 is to determine whether the suspected cancer cluster is a statistically significant excess. Several components of the follow-up investigation are necessary to determine if an excess of cancer cases exists in the community. These important components include the study design, as well as the collection, analysis, and interpretation of relevant data. Decisions must be made concerning the case definition, how the population of concern (the study population) is defined, the choice of comparison cancer rates, and the choice of statistical methods. To address these components, the health agency investigation team (the investigators) leading the follow-up investigation of Step 2 (and subsequent steps) will need to have epidemiologic expertise or collaborate with an epidemiologist. The time needed to complete Step 2 varies, depending on the complexity of the suspected cancer cluster.

This step also includes identification of local environmental concerns. Depending on the circumstances, communicating with partners and identifying and communicating with key community members about the assessment might be appropriate as a part of this step. Creating a comprehensive communication plan is important, in order to identify audiences, communication needs, and communication channels. More detailed information is provided elsewhere (see [Appendix B](#)).

Calculating a standardized incidence ratio (SIR) (23,24) is recommended at this step. The SIR is generally calculated to provide an estimate of the likelihood that an excess of cases exists in the population of concern (the study population) compared to the general or reference population. The SIR is a ratio of the number of observed cases to the number of expected cases. The observed cases are the cases that actually occurred in the study population within a specific timeframe. The expected number of cases is the number that would occur in the study population if the occurrence of cancer in that population was the same as the reference population. Since cancer rates vary with age, the expected number takes into account the age distribution in the study population. It is calculated by multiplying the age specific cancer incidence rates of the reference population by the corresponding age specific group in the study population. In the calculation of the SIR, factors that must be considered include:

- the type(s) of cancer and number of cases,
- the period of concern,
- the geographic area of concern,
- the background cancer incidence in the larger reference population (available through the cancer registry), and
- the demographic characteristics of the cases and the reference population.

More detailed information is provided (see [Appendix C](#)).

Procedures

- The investigators should define the study population, by demographic characteristics,

geographical area and time period of concern. These factors, in addition to cancer type, are also included in the case definition:

- Demographic characteristics might include age, sex, race/ethnicity, or residential location. The study population could be all-inclusive, or it could be limited to a specific demographic group. For example, the study population could include females only, adults only, or children only.
- The appropriate geographic area (study area) and time period need to be selected. Privacy issues should be considered when collecting, analyzing, and presenting data on a few cases in a small geographic area. Statistical analysis of neighborhood level data or data from sparsely populated areas might not be possible because of limited numbers. Limited numbers might lead to a lack of statistical power and therefore to an instability of rates. Decisions about timeframe and geographic boundaries should take into consideration the concerns of the caller or community, as well as any known or suspected environmental contamination and pathways of contamination (19).
- The case definition includes information on the type of cancer (e.g., primary site, histology, and grade). Cancer registries collect cancer diagnoses based on the ICD-O codes (International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3]) (25). Cases might be limited to a specific age or sex (e.g., limiting small cell lung cancer to women because the hypothesis is that there is an increase in the number of cases in women). Cases of cancer among the study population generally are identified from a state's cancer registry, using the case definition.
- An all-cancer SIR (i.e., one calculated for all types of cancers combined) might be useful for communication and educational purposes, but it is not useful for explaining or exploring potential etiologies. If an all-cancer SIR is presented with the results, a discussion of its limitations for investigating etiologies and its usefulness for cancer education should be included.
- The case definition, study population, study area, and period of interest will require justification. The definitions and the justification should be transparent to the community so that they understand the rationale behind the approach taken. This means sharing information that is consistent, timely, and expressed in a manner that the lay public is able to understand. Otherwise, these decisions might be seen as arbitrary and thus be rejected by the community.
- The investigators should calculate incidence rates, the SIR, and 95% confidence interval (CI) and other descriptive statistics. Procedural steps are discussed in detail elsewhere (see [Appendix C](#)).
 - An SIR of >1.0 indicates that the observed number of cases is greater than the number that would be expected for the population. The SIR increases when the number of observed cases in excess of the number of expected cases increases.
 - The CI is an indication of the statistical precision of the SIR value.
 - In addition to whether the SIR is statistically significant, the investigators should consider the suspected cluster in the context of the plausibility that the cancers could share a common etiology based on the latency, on community patterns of migration in and out, known risk factors for the cancer of concern, and the potential for exposure to a contaminant of concern, as well as other factors (see "[Decision to close the investigation at Step 2](#)").
- The investigator should understand community concerns and identify facts about local environmental factors by:
 - reviewing the literature on risk factors for the types of cancers in question, investigating both the human and animal studies using PubMed and/or other sources (e.g., <http://www.ncbi.nlm.nih.gov/pubmed>);
 - reviewing literature on possible associations between the types of cancers and known or suspected environmental exposures because results from the literature review might affect the case definition (e.g., the types of cancers considered for study); and
 - identifying whether there is concern in the community about known or suspected environmental exposures or other factors that the community suspects are related to health problems. By using the community members' "local knowledge" (i.e., understanding of the community, its history, and its members as distinct from the scientific/technical expertise

that is provided by health agencies) about the hazards and risk factors in their community, as well as data from environmental and other databases, investigators can make more informed decisions.

- The investigator should communicate with the inquirer and the community as indicated (see [Appendix B](#)). In many cases, communication about the activities in this step is only with the inquirer. However, if communitywide concerns exist about the cancer cases or environmental conditions, early involvement of other community members might be appropriate.
 - The investigator should share the SIR calculation with the inquirer and other community residents and describe the process, the results, and the implications of the results.
 - The investigator should consider who else should be notified after the SIR determination that there is, or is not, an excess number of cases (e.g., the local health agency, the state environmental agency, community residents).

Recommendations for Step 2

- Because of the variety of issues involved in this phase of the investigation, a team approach involving epidemiologists, toxicologists, communicators, and other experts might be necessary.
- Health agencies should document all decisions, communications, and processes.
- It might also be useful to examine the trend of a cancer type that is documented to be completely unrelated to the cancer type and/or exposure of concern. The purpose of this examination is to identify other factors that might affect trends or excess cancer cases detected. If all cancers appear elevated or depressed in a similar time frame (including those that are not related), other factors ought to be considered. These factors include the possibility that the estimated denominator might be incorrect or that the community has an unusually high proportion of persons with high-risk health behaviors (e.g., smoking).

Decision to Close the Investigation at Step 2

The decision to close the inquiry at this step or to move forward to Step 3 is based on multiple factors. The decision to move forward is best made on the basis of a review of the statistical analysis as well as an understanding of the scientific facts presented. To interpret the SIR, the health agency must answer these questions:

- Are there enough cases and a large enough population for statistical stability (17,23,26)? In general, the population size of a typical census tract (27) is the smallest denominator that will allow reliable results to be generated.
- If there is a large enough numerator for statistical stability, how likely is it that this SIR might have occurred by chance, assuming that the underlying incidence rates were not elevated (for example, does the 95% CI exclude 1.0)?
- Are there environmental contaminants and/or events that could be related to the cases?
- Are there any population-related issues (e.g., a substantial number of persons moving into the community) that might in part explain the observed cancer excess?

Other information in addition to the SIR is required to allow estimation of the likelihood that the observed cancers represent an excess, could potentially be related to one another, and share a common etiology. These questions include the following:

- Has there been an increase in the incidence rate of the specific cancer over time?
- How many more observed cases are there than expected (the number of excess cases)?
- Are the demographic characteristics of these cases unusual for the type of cancer (e.g., in a younger age group for a cancer [such as lung cancer] that usually occurs only in older age groups)?

The investigator needs the complete picture in order to determine the likelihood that the observed cancers represent an actual excess, could potentially be related to one another, and share a common etiology. An SIR of limited magnitude that is not statistically significant, coupled with a lack of known association with an environmental contaminant and no trend of increasing incidence over time, justifies closing the

inquiry at Step 2. However, a statistically significant SIR of great magnitude and an increasing trend in incidence rate, together with a known environmental contaminant would argue for continuing to Step 3.

The following examples illustrate how these data can be synthesized. For example, an SIR of <2.0 with CIs surrounding or overlapping 1.0 and/or a small number of cases (e.g., <10), coupled with limited evidence of an etiologic relationship between the type of cancer and the suspected environmental contaminant, might justify a decision to close the inquiry at Step 2. As another example, an SIR of >4 with CIs that do not overlap 1.0, and ≥ 10 cases that might be etiologically linked, should encourage advancing to Step 3. Moderate elevations in a SIR, involving small numbers of cases, and instances of rare cancers pose the most difficult decisions for health agencies. Additional information might be needed to assist in the decision to continue the investigation to the next step.

Once it is decided to close the inquiry at Step 2, it is important to respond to the caller in writing, explaining the process and results, including the determination that the cases likely do not comprise a cancer cluster. The inquiry should then be closed, with appropriate documentation in system logs.

Even if continuing with a cluster investigation is not indicated, the inquiry might have raised other concerns, including known or suspected environmental contamination. In that case, the health agency should work with partners to facilitate other public health actions or interventions, as warranted (e.g., health screening, health risk assessments, or education on cancer prevention). In these circumstances, it is important to communicate clearly with the community about the scientific basis for the actions, being careful to set realistic expectations for the community.

Some scientific experts have recommended implementing guidelines that use resources for cancer education and larger, long-term population based studies to determine risk factors for cancer rather than proceeding beyond Step 2 into cluster studies. This is because cluster studies almost never yield definitive answers regarding the cause of any specific cluster (28,29). Each health agency makes a decision as to what resources are available.

Decision to Continue to Step 3

Step 3 consists of gathering more information to assess the feasibility of conducting an epidemiologic study to determine whether the cases are associated with a common etiological factor. This process will engage additional resources and be more visible to the community. If a decision is made to move forward, the health agency should provide a written report to the caller, as well as to any partners contacted. This report should include a description of the results of the preliminary analyses and circumstances, carefully articulating what is known and not known at this point. Finally, the report should describe the health agency's plan (i.e., next steps).

Step 3. Determining Feasibility of Conducting an Epidemiologic Study

Description

The purpose of Step 3 is to assess the feasibility of performing an epidemiologic study to examine the association between the cancer cluster and a particular environmental contaminant. If further study is feasible, an outcome of this step should include a recommended study design.

All activities in this step should be carried out in collaboration with community, environmental, and other partners. Decisions should reflect the concerns, interests, and expertise of all partners. The health agency should follow the communication plan created in the previous step. This communication plan needs to be tailored to the community, and it should proactively address the information needs of stakeholders. It may be adapted as needed.

Additionally, this step provides the opportunity to evaluate additional public health actions, such as smoking cessation programs, cancer screenings, health risk assessments, removal of environmental hazards, or other activities that should be conducted. If beneficial to public health, these actions should not be delayed pending the decision to conduct or complete an epidemiologic study focused on assessing

the association between the cluster of cases and a suspected environmental cause.

Procedures

- The first actions in determining the feasibility of further study of the identified cluster include determining the study hypothesis and reviewing the scientific literature and past health agency reports.
 - The investigators should identify hypotheses. Past agency reports and logs should be reviewed to determine whether the same type of cancer has led to other inquiries and investigations. On the basis of preliminary findings, another literature search might be conducted (librarians at a public health library can assist with literature searches). A list of helpful resources is available at <http://phpartners.org>. The hypotheses should focus on known causes of the cancer in question.
 - The investigator should involve environmental, community, local public health, and other partners. The investigator should learn what the community needs and wants and assess the feasibility of addressing these concerns. The investigator should ask if partners know of any possible environmental risk factors in the area. The investigator also should discuss with the community whether there are issues of cultural sensitivity to consider in planning an investigation. A community panel is one method to involve the community. The investigators should define the panel's specific purpose and maintain open and frequent communication with the members. Advantages of a community panel also include gaining valuable information and diverse perspectives from members. However, it might be difficult to achieve consensus with such diverse membership. Finally, investigators should share information about time, cost, goals, purpose, and limitations of a potential study, with all partners and carefully communicate realistic expectations.
 - The health agency and its investigators should consider establishing an expert advisory panel to assess potential study design issues as sample size, a small case number, and study power. Health agencies should consider whether the panel contains internal experts from within the health agency or needs help from state government or external experts. Experienced scientists with appropriate skills should be included. The experts should include an epidemiologist, a toxicologist, a physician, an environmental protection specialist, and a community-nominated expert and/or local representative to provide advice on the assessment as needed. The panel's specific role, objectives, and deliverables will need to be defined.
- The investigators should identify such parameters as study population and its characteristics, including what descriptive, health, and risk factor data should be collected and determine the feasibility of obtaining that data. Investigators should:
 - confirm case diagnoses and determine which types of cancer and which cases meet the case definition,
 - identify a comparison group that depending on the study design does not have the cancer of concern (i.e. a control group in a case-control study) or does not have the exposure of concern (i.e. unexposed group in a cohort study),
 - consider the feasibility of obtaining data on individuals in the comparison group, and
 - explore the willingness of persons to participate in interviews or studies for gathering data on health, possible exposures, the amount of time the affected persons have lived in the area, and occupation. Investigators should also consider the ability to assess other relevant risk factors and confounding variables.
- The investigators should ascertain the plausibility that the cases and contaminants could potentially be associated. Specifically, they should:
 - verify whether the environmental contaminants of concern are known carcinogens,
 - consider possible and plausible routes of exposure to affected persons;
 - ask whether persons with cancer actually were exposed to an environmental contaminant in sufficient doses and for a sufficient time to make the association biologically plausible. On the basis of the consensus of the published literature, agencies should determine whether the exposure dose and duration were sufficient to have caused cancer, and they should ask whether the time sequence of exposure is consistent with the latency period and the causation of these particular cancers;

- consider the possibility that historical records of chemical use or contamination at the particular location might be more important than more recent environmental testing that might not reflect past contamination;
- determine whether residential and occupational histories for affected persons are obtainable. Information on a person's residential and occupational histories is of critical importance in constructing a complete exposure history. Investigators also should consider whether the person's occupation has a bearing on the total exposure.
- The investigators should identify the available data on the environmental contaminant of concern.
 - Environmental data can be helpful in cancer cluster investigations as part of the determination of the possibility of exposure to an environmental contaminant. However, it is generally not recommended to engage in a general, open-ended inquiry to identify potential contaminants in a community, in the absence of a suspected etiologic agent. Additional environmental testing should be carried out only when there is a clear scientific rationale and all the factors discussed below are considered.
 - Investigators should determine whether information on previous exposures is available. Because of the long latency of cancer, an historical exposure assessment might be more important than consideration of current exposures. Some exposures might have occurred >20 years previously. The suspected environmental contamination exposure period might span decades, and it might have changed during that time. In light of these factors, current environmental testing rarely provides accurate data on historical exposure.
 - Investigators should determine whether they can characterize exposure to suspected environmental hazards accurately at the individual level and in a way that reflects the period of concern.
 - Investigators should identify known current, ongoing, and historical environmental concerns in the community. The process of collecting such concerns also can have the benefit of enhancing their reliability and credibility with the community.
 - Investigators should partner with state and regional environmental protection specialists and toxicologists to secure aid in reviewing and interpreting historical exposure assessments. The investigator and subject matter experts should review historical environmental sampling data to determine whether there are any known or suspected area environmental contaminants that could potentially be related to cancer cases or are known or suspected carcinogens and whether there are any known or suspected exposure pathway(s).
 - Health agencies and their investigators should communicate with the public. At this point, the finding of an elevated rate of cancer in the community will likely be public knowledge, and the community might expect extensive environmental testing. There might also be pressure from the media or elected officials to perform new testing. Clear communication is critical to explaining why environmental testing is not feasible or not appropriate.
 - Investigators should assess information on possible exposures, not only for informing the design of a possible epidemiologic study but also for providing information for public health education, actions, or interventions that might be appropriate independently from an epidemiologic study (e.g., environmental testing to guide remediation efforts unrelated to the cancer of concern).
- Investigators should identify study design requirements and available resources to conduct the study. This process includes identifying the scope of the study and determining whether sufficient resources and data are available to complete meaningful work. Investigators should:
 - determine which parameters to use for geographic scope, study timeframe, and demographics and select a timeframe that allows for sufficient latency in cancers of concern;
 - determine the study design, sample size, and the statistical tests necessary to study the association as well as the effect of a smaller sample size on statistical power;
 - determine the appropriateness of the plan of analyses, including hypotheses to be tested as well as epidemiologic and policy implications; and
 - assess resource implications and requirements of the study and identify sources of funding.

Recommendations for Step 3

- Investigators should maintain communication with the community.
- Investigators should support the community through acting on an understanding that members might have valuable information about hazards in the area.
- Investigators should use a data-driven process for decision-making.
- Investigators should be proactive in maintaining interagency coordination and involving needed experts in advisory roles.
- Investigators should carry out the feasibility assessment as broadly as possible with existing information, including assessment of previous efforts in environmental or clinical testing.

Decision to Close the Investigation at Step 3

In some cases, despite the finding of a significantly elevated SIR, the feasibility assessment might indicate that further study will likely be unable to determine the cause of the elevated rate. In situations in which the types of cancers have no known association with an environmental contaminant, in which there are only a handful of cases, in which no suspected environmental hazard exists, or in which other factors explain the observed cancer excess (e.g., a substantial movement of residents during the study period), investigators might determine that data are insufficient or that insufficient justification exists for conducting further epidemiologic study. If the feasibility assessment suggests that little will be gained from proceeding further, the investigator should close the inquiry and summarize the results of this extensive process in a report to the initial caller and all other concerned parties.

In some circumstances, the public or the media might continue to demand further investigation, regardless of cost or biologic plausibility. Working with established community relationships, media contacts, and the advisory panel will be critical in managing and responding to expectations. If an extensive epidemiologic investigation is not carried out, it is critical to establish other possible options to support the community's health, depending on the information and resources available.

Decision to Continue to Step 4

If the activities in Step 3 to assess the feasibility of an epidemiologic study suggest that it is warranted, the responders should proceed to Step 4. Further outreach, health assessment, interventions, or other public health actions also might be appropriate. Conducting epidemiologic investigations can take several years; the health agency should consider what can be done in the interim to help protect the community's health and keep its members informed. This level of investigation often can be seen as research rather than public health response to a community concern. Providing periodic progress reports to keep the community involved can help overcome this perception.

Step 4. Conducting an Epidemiologic Investigation

Description

The primary purpose of conducting an epidemiologic investigation of the suspected cancer cluster is to determine if the exposure to a specific risk factor or environmental contaminant might be associated with the suspected cancer cluster. Demonstrating a statistically significant association does not prove causation. The scientific rigor necessary for determining causation is difficult to achieve with an epidemiologic study alone; in addition, determining causation often relies on clinical and laboratory studies (28). This distinction should be communicated to an audience not familiar with these methodologies.

Considerations

This step involves a standard epidemiologic study that tests a hypothesis of the association between putative exposures and specific cancer types, for which all the preceding effort has been preparatory. Using the feasibility assessment as a guide, responders should develop a protocol and implement the study. The circumstances of most epidemiologic studies tend to be unique. More specific guidelines are

provided (see [Appendix C](#)).

The results of an investigation are expected to contribute to epidemiologic and public health knowledge. This contribution might take a number of forms, including the demonstration that an association does or does not exist between exposure and disease, or the confirmation of previous findings. It could take many years for such studies to be completed, and even then the result often provides an incomplete picture.

However, even if a cancer cluster is identified and environmental contamination is identified, an investigation might not demonstrate a conclusive association between the contamination and cancer. Other risk factors (e.g., smoking, personal behavior, occupational exposures and genetic traits) also should be explored. Conversely, even if the investigation does not identify an association between a particular suspected environmental exposure and cancer cluster, the exposure still might be linked to the cluster; however, in such a case more scientific information might be required (e.g., toxicologic and clinical data) to establish an association. Epidemiologic studies alone often are not able to detect small effects, particularly in small populations or when the number of cases is limited.

Sometime in advance of beginning an extensive investigation, it is important that health agency responders and the investigation team be clear with the community, the media, and others about the inherent difficulties in undertaking such studies. Every effort should be made to set realistic expectations about the information an epidemiologic investigation will likely provide. Regardless of how exhaustive or comprehensive an investigation, few provide definitive answers and address the community's concerns. Even when expectations are established before the investigation begins, such circumstances can be disappointing to all, and particularly worrisome to the potentially affected persons. Thus after the investigation concludes, the health agency response often persists. Continuous interaction and relationship with the community, along with transparency of process, continue to be vital in such circumstances. Ongoing open communication, information sharing and public awareness efforts might be needed in order help the community overcome frustrating circumstances.

Conclusion

Public health agencies, including cancer registries, continue to receive hundreds of inquiries about suspected cancer clusters every year (10,14,29). Since publication of the 1990 Guidelines, many changes have taken place in data quality, technology, and communication. Data resources have become richer and statistical methods more refined, and many lessons have been learned from 2 decades of cancer cluster investigations.

Cancer cluster investigations continue to present many challenges. Populations at risk continue to be difficult to define, related environmental contaminants might have been in place many years earlier than the contaminant under investigation, and epidemiologic methods to provide strong evidence of association in large studies have limited value in community settings (14). Only a small fraction of cancer cluster inquiries might meet the statistical and etiological criteria to support a cluster investigation through all the steps outlined in this report. Because of the continuing challenges involved in investigating suspected cancer clusters, state and local health agencies continue to place an important emphasis on transparent and effective communication. The purpose of the revised guidelines contained in this report are to provide needed decision support to public health agencies in order to promote sound public health approaches, facilitate transparency and build community trust when responding to community cancer cluster concerns.

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