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Paul H. Levine
George Washington University

Salman Hashmi

Ashley A. Minaei

Carmela Veneroso

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Inflammatory breast cancer clusters: A hypothesis

Paul H Levine, Salman Hashmi, Ashley A Minaei, Carmela Veneroso

Paul H Levine, Salman Hashmi, Ashley A Minaei, Carmela Veneroso, Department of Epidemiology and Biostatistics, The George Washington University School of Public Health and Health Sciences, Washington, DC 20037, United States
Ashley A Minaei, University of Washington School of Medicine, Seattle, DC 98195, United States
Author contributions: Levine PH coordinated the study, prepared and finalized the manuscript; Hashmi S obtained information for the infectious agents portion of the manuscript, performed an extensive literature search of relevant papers, drafted part of the manuscript; Minaei AA obtained information on the carcinogenic chemical exposure relevant to the paper and drafted the relevant part of the paper; Veneroso C reviewed and edited all of the sections of the paper, made substantial improvements in the final version, and contributed important references and details for the manuscript.
Correspondence to: Paul H Levine, MD, Department of Epidemiology and Biostatistics, The George Washington University School of Public Health and Health Services, 950 New Hampshire Avenue NW, 5th Floor, Washington, DC 20052, United States. paulhlevine@earthlink.net
Telephone: +1-202-9945330 Fax: +1-202-9940082
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Abstract

Cancer clusters have long been a focus of interest because of the possibility of identifying etiologic agents. Only on rare occasions, however, have such cluster investigations been successful. One major difficulty in cluster investigations, particularly in the area of breast cancer, is the long latent period. There have been a number of publications providing a discouraging picture regarding cancer cluster investigations. The possibility of learning from a cluster investigation, however, is greatly increased if the cancer involved is relatively rare and if it has a short latent period. Inflammatory breast cancer (IBC) fits these criteria and is worth pursuing because of the strong evidence that environmental factors play a major role. In this report we describe our experience with several clusters and the lessons learned which are now being utilized to improve investigation of future IBC clusters. The first IBC cluster that we evaluated was in 2000, when we were asked to investigate an apparent cluster of IBC in Castro Valley, California where three women in an office setting of 24 people were diagnosed with IBC in a ten month period from May 1999 to March 2000. Our investigation of this striking cluster did not yield a specific trigger for this cluster but it did indicate that the women involved all had at least two IBC risk factors that may well have made them susceptible to getting IBC. We are now investigating another apparent cluster in Texas and are aware of several others requiring careful consideration. We see a need for a consistent protocol for the evaluation of IBC clusters focusing on the laboratory investigation of environmental triggers, primarily infectious agents and chemical carcinogens.

Key words: Inflammatory breast cancer; Environmental; Toxins; Infectious agents

Core tip: Cancer clusters are of interest because of the possibility of identifying etiologic agents. Such cluster investigations have been successful rarely. One major difficulty in the cluster investigations, particularly in the area of breast cancer, is the long latent period. The possibility of learning from a cluster investigation is greatly increased if the cancer is relatively rare and has a short latent period. Inflammatory breast cancer fits these criteria and is worth pursuing because of the strong evidence that environmental factors play a major role. In this report we describe our experience with several clusters and the lessons learned.

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INTRODUCTION

Cancer clusters have long been a focus of interest because of the possibility of identifying etiologic agents. Only on rare occasions, however, have such cluster investigations been successful[1-4]. In Goodman *et al*[5]'s review of 428 cancer cluster investigations in a particular geographic area or community, they found a confirmed increased incidence for only 72 investigations, of which only three were linked to the exposure, and in only one of those, the pleural cancer investigation in South Carolina, was there clear evidence that there was an exposure to some chemical in the naval shipyard[3]. In the other two investigations in which there was an association, there was statistical uncertainty. In the leukemia investigation in Woburn, Massachusetts, the association with contaminated water was not statistically significant and the association was found only in the boys and not the girls[1,6]. In the pediatric cluster in Dover Township, New Jersey[2], which was a superfund site, there were elevated incidences of leukemia and central nervous system cancers in children. However, a statistically significant association was found only with leukemia and for females only.

One major difficulty in cluster investigations, particularly in the area of breast cancer, is the long latent period. There have been a number of publications providing a discouraging picture regarding cancer cluster investigations[5,7-10]. The possibility of learning from a cluster investigation, however, is greatly increased if the cancer involved is relatively rare and if it has a short latent period. Inflammatory breast cancer (IBC) fits these criteria and is worth pursuing because of the strong evidence that environmental factors play a major role[11-13]. The evaluation of each cancer cluster is a separate experiment in which the outcome, while usually not identifying a specific etiologic factor, is a learning experience which can assist in preparing a more definitive evaluation when another cluster is identified. In this report we describe our experience with several clusters and the lessons learned which are now being utilized to improve investigation of future IBC clusters.

FOLLOW UP OF THE NILES, ILL. LEUKEMIA CLUSTER

The first cancer cluster we investigated was in 1967 when we were asked to obtain biological samples from the only survivor (JB) of a well described acute leukemia cluster in Niles, Ill.[14]. This cluster was the first of a series investigated by the Centers for Disease Control and involved acute leukemia occurring among children primarily in one Catholic school 1957-1963. These early studies were primarily descriptive although some biospecimens, primarily blood samples, were provided to the Viral Leukemia Section of the National Cancer Institute (NCI)[7]. The serologic tests available at that time were less specific than those in use today. In 1967 we learned that a survivor of the Niles, Ill. cluster, now 13 years old, was having a tonsillectomy and the virologists in the National Cancer Institute who were involved in the original cluster investigation hoped to obtain biospecimens from the tonsillectomy to isolate a leukemia virus. One of us (PHL) traveled to Chicago and obtained blood, bone marrow and tonsillar tissue placed in fresh media and brought them back to NCI for the laboratory studies. While no human leukemia virus was isolated from this patient, this and similar projects involving collection of biospecimens for NCI's Virus Cancer Program (VCP) proved to be valuable for years to come, providing reagents for research investigators, such as Robert Gallo, who credited the VCP with accelerating his discovery of human lymphotropic virus type I (HTLV- I) by providing appropriate biospecimens (Gallo, personal communication).

A CLUSTER OF CHRONIC FATIGUE SYNDROME ASSOCIATED WITH NON-HODGKIN'S LYMPHOMA IN NORTHERN NEVADA

A second cancer-related cluster that provided useful experience, although not IBC, was an outbreak of chronic fatigue syndrome (CFS) in 1984-6 in Incline Village, NV[15] which was focused on a single internal medicine practice since the two primary physicians were recognized as the regional experts on this controversial disorder. These physicians suspected an excess of cancer in their CFS patients, particularly non-Hodgkin's lymphoma and brain cancer, and asked for our epidemiologic assistance[16]. To investigate this possibility, we worked with the Nevada Cancer Registry and compared the cancer patterns in Washoe County in northern Nevada (which contains Reno) where the cluster was focused, to the patterns in Clark County in southern Nevada (which contains Las Vegas) which was selected as a control county. NHL and brain cancer were the targeted malignancies, and the control cancers chosen were breast and lung cancer. An abrupt relative increase in NHL was noted in 1986 in Washoe County compared to Clark County and a more sustained increase in brain cancer followed[17,18].

AN IBC CLUSTER IN CASTRO VALLEY, CALIFORNIA

The first IBC cluster that we evaluated[19] was in 2000, when we were asked to investigate an apparent cluster of IBC in Castro Valley, California where three women in an office setting of 24 people were diagnosed with IBC in a ten month period from May 1999 to March 2000.

The office had major environmental concerns. It was located one floor above a mammography and MRI imaging center and employees were concerned about the bad air and water quality in the office as well as the potential radiation exposure from the floor below. File boxes were stacked in front of windows that did not open in an area

where the ventilation system did not operate adequately when in use and was turned off at night. In addition, the office stored billing records printed on carbonless copy paper at a temperature above 68 degree Fahrenheit in the same area where the employees worked.

Although the complaints about the air and water quality and possible exposure to radiation began in 1986, the air quality studies and a water sampling study did not begin until 1988 and the radiation leakage studies began in 1999 when new mammography equipment had replaced the old units. The water sampling studies indicated that the only organic compounds detected were present at allowable California maximum contaminant levels. The radiation leakage studies found no radiation despite the absence of concrete between the two floors. The indoor air quality studies showed that the office had poor air circulation and higher levels of CO and CO_2. All three cases had their offices located on the side of the office that had the worst air circulation according to the studies.

All employees were interviewed by telephone using a structured questionnaire that obtained demographic information and information on IBC and breast cancer risk factors, such as pregnancy history, family history of breast cancer, oral contraceptive and hormone replacement therapy use, medical history, and exposure to possible oncogenic agents and tumor promoters.

The three cases did not live in the same residential area and therefore did not share the same residential environmental exposures. While the sample was too small to do statistical analyses, there were some interesting differences between the cases and the controls. The cases had a higher BMI, higher oral contraceptive and hormone replacement therapy use, and were exposed to pesticides and herbicides for a longer period of time. The one case that had children had her first child at age 19 and did not breast feed her children. Two of the cases had a family history of breast cancer, and the third case's mother was adopted.

All three cases were seen by the same oncologist and all cases had pathologically confirmed IBC with invasion of the dermal lymphatics. Although IBC is a clinical diagnosis and pathologic confirmation is not necessary, the surgeon believed documentation was important and obtained skin biopsies. It required 15 skin biopsies before a positive skin biopsy was obtained for one of the cases. We obtained tissue samples for all three cases.

Our attention was focused on the environmental exposures because of the concerns of the office workers and at that time infectious agents were not considered.

AN IBC CLUSTER IN FRIENDSWOOD, TEXAS

In 2011, a possible IBC cluster in Harris and Galveston counties in Texas was brought to our attention by a patient advocate/IBC survivor as part of our recruitment of cases for the IBC Registry and a biospecimen repository, which we established in 2002[20]. The registry links epidemiologic information with laboratory studies from our biospecimens. We were referred to an IBC Google map (www.terrysmap.org) that reports IBC cases in the United States and is constantly updated. The IBC map showed approximately fifteen cases diagnosed between 1998 and 2011, nine in Harris County and six in Galveston County. All women in this apparent cluster were diagnosed at major cancer centers in the Houston area, including the MD Anderson Medical Center.

We were encouraged by the patient advocate/IBC survivor to enroll these patients in our Registry which only enrolls patients who contact us first and complete Informed Consent forms as per our Institutional Review Board (IRB) approval. Based on information from concerned patients, one focus of research was a hazardous waste site designated by the Environmental Protection Agency (EPA) which allegedly had waste draining into a stream going through the community. In order to investigate possible environmental triggers for this IBC cluster, we tried to identify the potential hazardous waste sites in the region utilizing the National Priorities List (NPL) developed by the Environmental Protection Agency (EPA)[21]. Harris County with its largest concentration of chemical manufacturing and refining facilities has 27 EPA regulated Superfund Sites out of 31 for both counties. Key concerns regarding the quality of outdoor air include elevated levels of ozone and particulate matter. Two seafood advisories have been issued in the past for the Galveston bay system, tributaries of which run through parts of both the counties. The first was based on dioxin contamination. The second advisory was based on the three toxic compounds, namely dichloromethane, trichloroethane (carcinogens) and carbon disulfide discovered in fish from Clear Creek, a principal tributary of the Galveston bay. The contaminated fish were found in the vicinity of an EPA Superfund site. A study of the map showed two cases in the Friendswood city where the Clear Creek flows and which also includes a former refining site. Four cases were also concentrated near Clear Lake in Galveston County.

As this cluster was being investigated, the possibility of an infectious trigger was raised by a report suggesting infectious agents as possible etiologic factors in a series of IBC patients in Pennsylvania[22] and our observation of a seasonal incidence of IBC in the northeastern United States[13]. We therefore investigated infectious agents prevalent in Harris County where this IBC cluster appeared, and noted that Saint Louis encephalitis (SLE) is endemic and occasionally epidemic in that particular region. In 2002, West Nile virus (WNV) appeared in Houston and quickly spread throughout that region. Both SLE and WNV are transmitted by a particular species of mosquitoes, called *Culex quinquefasciatus* which is the prevalent species in Harris County. It is also a dominant vector of lymphatic filiriasis, a disease caused by thread like parasitic worms. This raises the possibility of a parasite or a virus transmitted by mosquitoes. *Culex quinquefasciatus* larvae breed and thrive abundantly in stagnant dirty

water. The elaborate drainage system of Harris County creates ideal biotic and abiotic conditions conducive for mosquito larval development, particularly during relatively dry periods when stagnant water remains in the storm sewer system. Approximately 99% of the mosquitoes that develop in these storm sewers are *Culex quinquefasciatus*. These mosquitoes use the storm drains as daytime resting sites as well as for larval development. Outbreaks of *Vibrio* diseases have also been reported. Out of 176 *Vibrio* infections reported statewide between May of 1981 and September of 1991, 68 were reported in counties surrounding Galveston Bay which also includes Harris County. Contact recreation and consumption of molluscan shellfish, primarily oysters, were roughly equal sources of Vibrio infections, which accounted for 75% of the reported cases. The consumption of oysters, especially raw, can pose a significant health risk since oysters can concentrate pathogens in their gut as they feed. Of particular concern is Vibrio Vulnificus, which can cause severe infection with exposure of open wounds to sea water, especially in those with underlying chronic diseases or who are immunocompromised. This particular bacterium showed a greater genetic diversity in Galveston Bay water and oysters. An interesting feature of this organism is its response to low temperature stress where it goes into a viable but non-culturable state during winter months (December to February). These observations are intended to show the feasibility of infectious agents as a trigger to the Texas cluster but no evidence for such a link currently exists.

An attempt has been made to confirm the reported IBC cases and to get updated information from the Texas Cancer Registry, comparing the incidence of IBC in the Houston area with other metropolitan areas, such as Dallas and Austin. These studies are in progress.

DISCUSSION

Cancer clusters are notoriously difficult to evaluate, and we have tried to take advantage of our experience and those of others to develop a hypothesis consistent with the information currently available on IBC. One hypothesis that we believe is tenable is based on our studies of CFS and NHL where a cluster of CFS showed an ecologic association to NHL[16,17,23] and the link was subsequently documented by a linkage of population-based registries of CFS patients in Medicare and cancer patients in SEER[24], where NHL was the only malignancy with a statistically significant association with CFS. The virus most closely linked to CFS is EBV, which is consistently reactivated in those patients with acute onset CFS presenting with an infectious illness[25], and, not infrequently, is a long term sequel of infectious mononucleosis which is the most common clinical manifestation of primary EBV infection. EBV is a ubiquitous virus, however, and more than 90% of the population has been infected early in life and is therefore immune to new infection. Therefore EBV is unlikely to trigger a cluster of CFS. Since CFS can be triggered by a variety of infectious agents[26], we hypothesize that a new agent struck the community and in certain susceptible individuals, perhaps those with a predisposing susceptibility to an autoimmune disorder, CFS developed. Clusters of CFS (initially described as epidemic neuromyasthenia)[27,28] have been well documented[29] and occasionally the precipitating agent has been identified, including EBV, herpes simplex-1, herpes zoster and giardia[26,30]. We therefore postulate that for IBC, it is feasible that a precipitating agent, either chemical or infectious, could strike a community and those individuals with a predisposition (possibly a combination of factors such as obesity, family history, and/or infection with the proposed human tumor virus with sequences similar to mouse mammary tumor virus[31-34], subsequently develop IBC. While we were successful utilizing the Nevada Cancer Registry to show the clustering of NHL after CFS, similar efforts investigating IBC is very problematic. NHL is a defined disease histologically and should be captured by a cancer registry in virtually 100% of cases. IBC, however, is a far more difficult problem for two reasons. First, the diagnosis has been evolving, and, although the situation has improved since we first documented the conflict between two major institutions, the American Joint Committee on Cancer and NCI's the Surveillance, Epidemiology, and End Results program (SEER), who used different case definitions[20], the situation is far from satisfactory. Our clinical experience in Tunisia and with the IBC Registry indicates even the current criterion of clinical involvement of one third of the breast is too restrictive and the diagnosis should be made in any patient with acute onset of erythema, induration, and/or peau d'orange regardless of the size. This suggestion is supported by research efforts documenting the similar outcome and laboratory findings in IBC regardless of the extent of erythema[35,36]. Second, there are many reasons why IBC may not be recorded in the cancer registry even though the physician has the diagnosis in his office records because it may not be noted by the abstracter reviewing the final hospital diagnoses. Attempts are being made to investigate the degree of "slippage" between the number of cases identified by practicing physicians and the number of cases recorded in the central registry[37]. In addition to the concern that many IBC cases are not appropriately coded in cancer registries, there are constraints that hinder the collection of data on IBC in small geographic areas, even counties, since registries often will not release data where less than 50 patients are included because of concerns about confidentiality being maintained.

Although the extensive experience of the Centers for Disease control[7] and others have often been disappointing, investigation of clusters of rare aggressive cancers such as IBC should not be completely neglected. For optimal pursuit of such clusters, several items should be considered to bring optimal results.

The importance of a coordinating physician(s)

Coordinating physicians were extremely important in the

success of cluster evaluations in Niles, Ill (the patient' s internist), Incline Village, NV (the two internists in the practice) and Castro Valley, California (the three patients' medical oncologist). These physicians facilitated the signing of the informed consent forms, documentation of diagnosis, collection of good historical data, and collection of biospecimens. In contrast, thus far the absence of a coordinating physician in Texas has made interviews of the patients and collection of biospecimens in the Texas cluster extremely difficult.

Preservation of biospecimens

Obtaining biospecimens is critical. Techniques for utilizing a variety of biospecimens, including formalin fixed paraffin embedded tissues, in molecular studies continue to improve. We have been able to use the biospecimens in our repository for a number of projects[36,38-40] and several hypotheses can be proven with these samples, such as the detection of organochlorines should chemical toxicity be responsible for the Friendswood clusters. In future studies, blood samples on cases and controls should be obtained to investigate the possibility of infectious agents as triggers of clusters. Other hypotheses might require other biospecimens, such as saliva or urine.

The importance of moving quickly

Early investigation is critical because of the frequently poor outcome in IBC. For example, our prompt investigation of the Castro Valley cluster allowed us to obtain a critical positive family history not recognized by clinicians from a patient who died shortly after our interview. Ideally one should obtain the biospecimen before treatment as neoadjuvant chemotherapy may affect the tumor biology.

Identification of appropriate laboratory support

The thorough evaluation of biological specimens requires experienced laboratory support that is primarily found in large research institutions. As noted below, it will be useful to have consistent protocol for the evaluation of IBC clusters to allow an exchange of relevant information among various investigators. We are currently attempting to develop a protocol focusing on infectious agents and environmental toxins with potential carcinogenic properties but we expect this protocol to change as laboratory techniques improve and additional information is obtained from other cluster investigations. Our latest studies are taking advantage of available molecular techniques allowing identification of bacterial pathogens in paraffin blocks of tumors but we expect eventually to explore viral pathogens and collect blood samples for antibody studies. The identification of potential toxins will be difficult because they are rapidly metabolized and/or excreted but we hope to identify some persistent chemical byproducts, such as organochlorines, which may be useful.

The issue of statistical significance

Statistical analysis of cancer clusters has been addressed in several publications[41,42] and various analytic methods have been used, but it is important to recognize that biological significance can be independent from statistical significance. Statistical significance is particularly problematic because of the small number of IBC cases compounded by changes in the case definition and Registry coding. Occasional misdiagnosis or unusual presentations have been encountered[43-47], but these are uncommon and are unlikely to deter epidemiologists from focusing laboratory studies on the typical cases. We suggest that the identification of a cluster of IBC cases in a short period of time, such as the three women in a small office within ten months, deserves investigation regardless of whether or not it is statistically significant.

CONCLUSION

In summary, the apparent importance of environmental factors on the etiology of IBC and the identification of clusters of this relatively rare aggressive malignancy indicate the need to investigate these clusters for possible etiologic triggers. A variety of biospecimens should be collected for immediate testing but also for storage as future hypotheses and technology may provide clues not initially apparent. Tissue samples could be examined for toxic chemicals or infectious agents, blood samples could be used to identify adducts signifying exposure to carcinogens or antibodies to infectious agents, and DNA (saliva or white blood cells) could be used to identify genetic markers of susceptibility. Detailed histories could not only reveal potential important exposures but systemically applied questionnaires such as those used by the IBC Registry could identify predisposing factors that could add to our understanding of risk factors for IBC.

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