Pancreatic Cancer Follow-up Investigation Report, Oroville area, Butte County

Environmental Health Investigations Branch (EHIB)
California Department of Public Health (CDPH)

March 2009

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EXECUTIVE SUMMARY

The Environmental Health Investigations Branch (EHIB) of the California Department of Public Health (CDPH) conducted a follow-up investigation of pancreatic cancer cases in the Oroville area of Butte County. The California Cancer Registry (CCR), a program of the Cancer Surveillance and Research Branch of CDPH, had identified a statistical excess (more cases than expected) for the years 2004-2005 in an evaluation of pancreatic cancer incidence in the area conducted in response to a resident's concern about a perceived excess. Although the number of cases in earlier years was not unusual, CCR estimated that twice as many cases occurred as would be expected for this two-year period. The resident also shared concerns about a link to environmental exposures, in particular a fire that occurred in 1987 at a now-closed wood treatment facility in Oroville.

Pancreatic cancer is the fourth-leading cause of cancer-related death. It is difficult to find early because it is not detectable on routine exams, and symptoms tend to be non-specific and not very noticeable until the cancer is in later stages. The average age at the time pancreatic cancer is diagnosed is 72.

The Butte County Public Health Department and EHIB sought to interview the cases in order to determine if they shared experiences or characteristics (e.g. unusual exposures, known risk factors or possible environmental/occupational factors) that might suggest why the excess occurred. There were 24 cases in the 2004 – 2005 time period, and we also included nine cases that had been diagnosed in 2006 at the time of the investigation, although reporting for that year was not yet complete, for a total of 33 cases. We were able to contact and interview 25 of these 33 cases or their next-of-kin.

Since the time the investigation was conducted, an additional case was reported that had been diagnosed in 2006. The ten cases in 2006 are fewer than the number of cases occurring in the years 2004 or 2005, but still greater than the expected number per year. However, if ten cases had occurred in 2006 without elevations in nearby years, this would not appear to be out of the ordinary.

The demographic characteristics of the group were not unusual, and typical pancreatic cancer risk factors were common, including: diabetes; family history of diabetes and cancer, particularly pancreatic cancer; and tobacco use.

Although a variety of possible environmental and occupational exposures were noted, none were consistently found among enough members of the group to explain the occurrence of the excess. For example, some members of the group reported occupations such as mechanics or welders or exposures like pesticides that may have increased their risk for pancreatic cancer. Locally caught fish were generally not eaten. Only one case had ever worked at the wood treatment facility; only two lived in an area evacuated during the fire; and the only person

who may have consumed well water from the groundwater plume was the former worker.

Specific causes for most community cancer clusters are rarely found. If the thousands of communities in the state are considered, it is almost certain that some will have higher than normal cancer rates by chance. However, barriers that make it difficult to recognize an environmentally caused cancer excess, if one were to exist, include: the long latency period; the different exposures that can cause the same cancer; and incomplete information regarding past exposures. Cancer is not directly tied to one cause the way an infectious disease is caused by a specific bacterium or virus, and is usually caused by a combination of multiple factors.

In conclusion, we performed an extensive field investigation and data review and found no common factor among the cases that could plausibly account for an excess of pancreatic cancers. Many cases shared a known risk factor for pancreatic cancer (such as smoking, being overweight, having diabetes, or a family history of pancreatic cancer), and some worked at specific occupations that may be linked to pancreatic cancer (such as mechanic, welding, working with pesticides), but no widespread exposure or unusual Oroville circumstances appeared responsible for the community wide excess.

We recommend continued monitoring of the occurrence of pancreatic cancer for the next few years to determine if the number of cases returns to within the expected range, as is suggested by the decline in more recent data, or whether an excess persists.

INTRODUCTION

This report describes a follow-up investigation by the Environmental Health Investigations Branch (EHIB) of the California Department of Public Health (CDPH) of an apparent excess of pancreatic cancer cases in the Oroville area of Butte County. Prior to this report, the California Cancer Registry (CCR), a program of the Cancer Surveillance and Research Branch of CDPH reviewed existing data to evaluate pancreatic cancer incidence in the area in response to a resident's concern about a perceived excess, and found a statistical excess (more cases than expected) for the years 2004-2005.[1]

In their data review, CCR calculated the expected number of pancreatic cancers for the years between 1988-2005, given the size and demographic characteristics of the population. Although the numbers of cases in the earlier years were not unusual, between 2004 and 2005, CCR estimated that twice as many cases occurred as would be expected for this two-year period. Data were incomplete for 2006 at the time and were not included in that report, released in January 2008.

The resident reported concerns about possible environmental exposures, in particular a fire that occurred in 1987 at the now-closed Koppers Industries wood treatment facility in Oroville.[2] To determine whether there were any common factors that may have led to the occurrence of an excess number of cases at the time and place, CCR referred the issue to EHIB for further investigation. This was in accordance with CDPH procedures for situations in which an excess has been identified and where there are concerns about whether chemical environmental exposures may have contributed.

Project goals

- To respond actively to concerns raised by community members in the Oroville area regarding the pancreatic cancer excess by conducting a follow-up field investigation to interview individuals in the group or their next-of-kin.

- To determine if any unusual commonalities or other reasons, such as known risk factors or possible environmental/occupational factors, can be identified that may suggest why the excess occurred.

- To gather information about the characteristics of the persons in the group of cases with pancreatic cancer to help inform whether any additional public health or research activities are warranted and useful.

BACKGROUND

Pancreatic cancer

Pancreatic cancer is a malignant tumor within the pancreas, an organ about six inches long behind the stomach. Pancreatic cancer has been called a "silent" disease because pancreatic cancer usually does not cause noticeable symptoms until later stages. This cancer is the fourth-leading cause of cancer-related death in the United States.[3]

The pancreas is a gland that makes digestive juices and hormones, including insulin. There are two types of pancreatic cancer, exocrine and endocrine. The cells in the exocrine gland secrete pancreatic “juice” which contains digestive enzymes. The endocrine cells produce hormones, including insulin, that help regulate the amount of sugar in the blood. Exocrine tumors are much more common, and typically account for more than 95% of cases.[3] Nationally, the lifetime risk of developing pancreatic cancer is 1 in 75.[4] The average age at the time the cancer is found is 72.

Pancreatic cancer is difficult to find early because the pancreas is deep inside the body, and tumors cannot be seen or felt during routine physical exams.[5] Also, many of the symptoms of pancreatic cancer are not very specific, such as back pain, digestive tract problems such as abdominal pain, nausea, diarrhea, and constipation, and sleeping disorders. Other symptoms include loss of appetite, weight loss, jaundice, and uncontrollable itching. By the time a person has symptoms the cancer may be large and have spread to other organs. Additional information about diagnosis, risk reduction, and resources regarding pancreatic cancer can be found in Appendix B.

Known risk factors

Little is known about the exact causes of pancreatic cancer. However, there are some things that increase a person’s risk, including:[6]

- Smoking – The most generally accepted risk factor for pancreatic cancer, and accounts for about 30% of cases
- Inherited characteristics – Family history accounts for up to 10% of cases
- Gender – Men are slightly at greater risk, perhaps due to smoking patterns
- Race – African Americans are at greater risk
- Diet – High consumption of meat and fat
- Obesity
- Diabetes – Long-term diabetes increases risk, although diabetes may also be a symptom of early stages of pancreatic cancer

Pancreatic cancer – possible environmental or occupational exposure factors

The overall contribution of occupational exposures as causes of pancreatic cancer is thought to be low, as rates of pancreatic cancer are similar between industrialized urban regions and rural areas.[7] Studies of occupational exposures have had varied results and have not found strong associations with pancreatic cancer. However, exposures to certain groups of chemicals among people who work with these chemicals may be associated with pancreatic cancer. These include some members of a large class of chemicals called chlorinated hydrocarbons that are made from petroleum products, another group called PAHs (Polycyclic Aromatic Hydrocarbons), and nitrosamines.[7]

Chlorinated hydrocarbons are found in solvents, certain paints, glues, and dry cleaning solutions. PAHs occur in tobacco smoke, coal tar, crude oil, and creosote; are produced when substances like coal, oil, garbage, and meats are burned; and are used to make certain dyes, plastics, and pesticides. Nitrosamines are compounds found in tobacco smoke and cured meat products, as well as in oils and fluids used in metalworking.

Other exposures for which there is some suggestion of an association with pancreatic cancer risk - although this association is yet less firm than those mentioned above - include occupations involving working with metals, such as nickel and chromium, and work in paper and pulp mills.

Koppers wood treatment facility

Koppers Industries, Inc. owned a wood treatment facility which operated in the South Oroville area between 1955 and 1988.[2] One of the main operations at Koppers was the pressure-treatment of wood with pentachlorophenol (PCP). PCP can be contaminated with dioxins, and PCP and dioxins are either known or probable carcinogens as well as have a number of other toxic properties.

The Koppers facility had a history of contaminating the ground water with PCP. In 1981, a number of domestic private wells were found to be contaminated, and residents were provided with bottled water, although they continued to use well water for bathing, irrigation, and livestock. The contamination did not affect the public water supply, and in 1986, residents with contaminated wells were connected to the public water supply. Since then, water testing has shown that the private well contamination has improved.

The 1987 fire at the Koppers facility burned PCP over a six hour period, and a voluntary evacuation advisory was issued to residents in an area approximately two by three miles south of Oroville, while CDPH tested the soil and vegetation for PCP and dioxins (dioxins can be formed during some combustion processes).

Testing by CDPH found that it was safe for people and pets to come into contact with the soil and safe to eat home grown fruits and vegetables, and several days later the evacuation was lifted.

However, as part of the environmental testing after the fire, CDPH testing of chicken eggs and meat from a cow showed dioxin contamination.[8] Further investigations, including testing of frozen animal products and other types of environmental samples, suggested that the contamination predated the fire and that chickens were exposed through contact with soil.[9] In 2000, an advisory was issued to the greater Oroville area (including South Oroville, Palermo, and Thermalito) advising residents not to eat eggs and meat from chickens that forage on the ground.[10] Results from subsequent studies in other areas suggest that eggs from chickens foraging on ground anywhere in California may have higher levels of dioxins than commercial eggs, which are generally raised without contact with soil.[11]

In 2000, the U.S. Agency for Toxic Substances and Disease Registry reviewed the existing data on the former Koppers site and determined that the site did not pose a current public health hazard.[2]

METHODS

Case definition

The criteria for inclusion in the investigation were: all cases recorded in the Registry, diagnosed in 2004-2006 with an address in Butte County census tracts 0025.00 through 0033.00 at time of diagnosis, where:

1) Pancreatic cancer was the first malignancy; or

2) Pancreatic cancer was the second or higher malignancy, if the case was microscopically confirmed (SEER site recode 21100).

I. Field investigation

The main effort of our field investigation was to gather and analyze additional, detailed information not routinely collected by the CCR by interviewing cases or their next-of-kin.

Contacting cases and next of kin

Persons who had been diagnosed with pancreatic cancer, as designated by the CCR (or their next of kin, if deceased), were sent letters explaining the follow-up investigation and requesting their participation.

We followed up letters with phone calls, if a phone number was available. We made at least three attempts to contact next-of-kin with working phone numbers

who, to our knowledge, were not deceased. If we reached someone else, we asked if that person knew how to contact the person we were seeking.

If no phone number was available or if the number turned out to be incorrect, we searched directory assistance and a professional service for phone numbers and addresses (Accurint,® a proprietary locate-and-research tool, http://accurint.com/). If no phone number could be identified but an address for the next-of-kin was available, we sent a letter requesting that the person contact us.

We also contacted physicians of persons of cases to inform them of our efforts in the community. For persons for whom we did not have the name of next-of-kin, we asked the physician to provide one, if possible.

Conducting interviews

Cases/next-of-kin were given the option of interviewing in person at their home (if in the Oroville area), at the Butte County Public Health office, or by telephone. Interviews were conducted by Butte County and EHIB staff.

The interviewer reviewed the purpose of the investigation, what participation involved, the voluntary nature of participation, and the confidentiality of participation. Interviewees signed consent forms if the interview was conducted in person; otherwise, the content was reviewed orally during the phone interview and oral consent was obtained prior to the interview.

Contents of questionnaire

The questionnaire was designed to elicit possible relevant factors that may be common among cases. It included basic demographics and background medical history, including past cancers and other significant medical conditions, particularly those which have been shown to be associated with pancreatic cancer. Information on occupations, hobbies, lifestyle, family medical history, and other risk factors were collected. We calculated Body Mass Index (BMI), a measurement of obesity that takes into account height and weight. Dietary questions included alcohol consumption, although evidence for alcohol being a cause of pancreatic cancer is weak; if it has any role, it may be among heavy drinkers because they have increased risk for pancreatitis, a risk factor for pancreatic cancer.

We asked about previous occupations and hobbies or activities outside of work, especially those that may have involved exposures to hazardous substances.

Possible environmental exposures were queried, particularly exposures specific to the Oroville area. This included an assessment of water source and potential exposure to the groundwater PCP plume from Koppers. We reviewed and mapped every Oroville residential and worksite address in which the respondent reported that the water source had been well water, and compared the location to

the PCP plume from Koppers. If the respondent was not sure if private well water was used, those locations were also compared. Also, possible exposure to the Koppers fire, consumption of locally raised produce (due to concern about the dioxin advisory), and other environmental exposures, such as smoke from burning chemically treated wood or rice burning practices, were considered.

II. Update previous review of pancreatic cancer excess

Question 1: Are there more cases of pancreatic cancer in the Oroville area during 2006 than would be expected?

We checked for all additional cases from 2006 that had been reported since the 2004 - 2005 time period reported by CCR.

III. Review cases to determine if unusual

We summarized and analyzed the information from the interviews in several ways to see if there were patterns in characteristics or risk factors among the group of cases. The rationale for this is that an unusual environmental exposure that would cause a sudden near-doubling of cases community wide would produce a large fraction of cases that did not fit the usual pattern of pancreatic cancer cases, or have the typical risk factors, but who shared an unusual history.

Question 2. Are the cases during the 2004-2006 period unusual?
2a. Are the cases unusual compared to the Oroville area cases from the previous four years?

We conducted an evaluation based on existing data available from CCR to see if cases in the period of excess were different from cases diagnosed from the same area in earlier years when there was no excess. We compared characteristics of cases from the time period of excess cases, 2004-2005, plus the more recently available 2006 cases, to the cases from the same community diagnosed in four prior years, 2000-2003.

The differences in the case characteristics, such as sex, age at diagnosis, race, and socioeconomic status (SES) were evaluated statistically with a chi-square test for two-way contingency tables, or an exact test when expected cell frequencies were less than one.[12] SES was ranked using an index from 1 (low SES) to 5 (high SES) based on information from the census.[13] We also evaluated the type of pancreatic cancer (endocrine or exocrine) and the stage of cancer at diagnosis, which may show trends in how advanced the disease was at the time of diagnosis.

2b. Do the cases have accepted risk factors for pancreatic cancer in the typical frequencies?

- Overview of descriptive information on typical pancreatic cancer risk factors.

We summarized the information on the cases to get a general description of the group, and in particular looked for any characteristics or factors that seemed unusual about the group as a whole.

- Comparison with other pancreatic cancer cases

We also reviewed information in light of what is known about risk factors for pancreatic cancer, using other studies to help interpret our findings and evaluate whether the profile of risk factors in the Oroville cases was unusual or not. We compared our findings with those from a variety of large case-control studies of persons with pancreatic cancer, including studies by the research group led by Dr. Elizabeth Holly at the University of California in San Francisco. Dr. Holly has conducted one of the largest population studies, including over 500 persons with pancreatic cancer.

2c. Do the cases share environmental, occupational, or other risk factor(s) to the extent that could plausibly account for the excess?

- Overview of potential environmental and occupational exposures

We reviewed environmental and occupational risk factors noted, particularly those that were possibly specific to the Oroville area.

All jobs reported, including those from early in life or held for relatively brief periods of time, were classified using the U.S. Census 2000 Index of Occupations.[14]

We reviewed the occupational history, exposures, and hobbies of the cases based on the types of occupations and exposures that have shown some association with pancreatic cancer in scientific literature, although these links were not always clearly established.[7] An industrial hygienist initially categorized all occupations and assessed the likelihood of a variety of exposures; this was then reviewed and adjusted if needed by a toxicologist.

The occupations or exposures considered included: sedentary occupations; ionizing radiation; asbestos; metal; polycyclic aromatic hydrocarbons (PAHs) and nitrosamines; chlorinated hydrocarbons; other pesticides; other chemicals/occupations, and some more specific sub-categories of these groups.

- Comparison with predicted prevalence of risk factor among cases

Given that a main purpose of this investigation is to determine whether an environmental factor in the Oroville area could be responsible for the excess number of cases seen, what specifically are we looking for when we examine the cases? We are looking to see whether the purported risk factor is shared by enough members of the case group to plausibly explain the excess.

We know that the pancreatic cancer incidence in Oroville was 1.8 times greater than expected from the rate in the surrounding cancer registry region. If a single exposure in Oroville were responsible for the increased cancer rate, how strong a pancreatic cancer risk factor must it be, and how prevalent in the community, in order to account for this increased incidence? To answer this, we examine the incidence of the disease in the population we are studying relative to a comparison population – this is the SIR (Standardized Incidence Ratio). The SIR is a combination of the strength of the risk factor and the prevalence of the risk factor in the community.

We calculate how common a risk factor must be (its prevalence) in order for it to produce a given SIR. The formula to do this is given in Appendix B. In looking at the reported risk factors for pancreatic cancer, such as smoking, most have relative risks (RRs) in the range of 1.5 to 3. The strongest, such as having a family history of pancreatic cancer, is around 5.[15] For risk factors which are not present, or very rarely present, outside Oroville, at least 50% of Oroville cases would have to share that exposure. For more common risk factors, two-thirds or more of the cases would have to share that factor. Therefore, an exposure seen in only one or two cases is not sufficient to account for a near doubling of the community-wide rate.

Thus, in advance of analyzing the case series, we can estimate the prevalence among the cases which a risk factor would need to have in order to be a possible cause. The table below gives values for the prevalence of exposure in the Oroville-area population, and the fraction of the cases that would be exposed, for risk factors that span the range of reported risk factors for pancreatic cancer, in order to produce the Oroville-observed SIR of 1.8.

Table 1: Predicted prevalence of possible environmental or other factor among cases as a guideline for interpretation of relevance of factor in accounting for excess, given the observed Oroville-area SIR = 1.8

RR of exposure factor	Prevalence of factor in reference area	Prevalence of factor in Oroville population	Prevalence of factor among Oroville cases
2	0	80%	89%
2	10%	98%	99%
3	0	40%	67%
3	20%	76%	90%
5	0	20%	56%
5	20%	56%	86%

The last column represents the proportion of cases from the group of cases with the risk factor that we would expect to see, if in fact it were responsible for the excess.

RESULTS

I. Participation in investigation

CCR identified 33 cases that met the case criteria (Table 2). Of those, 13 were diagnosed in 2004, 11 in 2005, and nine in 2006. We interviewed 25 cases or next of kin, for a participation rate of 76%. There were generally positive reactions to our investigation attempts. Reasons that not all interviews could be conducted included: one case was too ill to be interviewed and the next-of-kin declined; another had only moved to Oroville after becoming ill and a few weeks prior to diagnosis, and thus this information would not have been related to a common cluster; and we were unable to reach the rest. Out of the 25 case interviews completed, two were conducted with the patient, 11 with a spouse, and 12 with another next of kin. Most of the cases (88%) had lived in the Oroville area for at least 10 years prior to diagnosis, with 40% living in the Oroville area for 30 years or more.

We also conducted several interviews for cases that were not in the case definition but whose next-of-kin contacted either the state or county health department and asked to be included. The information gained from these additional interviews was reviewed separately from the cases in the period of excess to see if there were any common factors or distinguishing characteristics among or between them.

Table 2: Participation in the follow up investigation of pancreatic cancer

	Identified by CCR criteria (n)	Next of kin contacted health department (n)	Total (n)
Total cases identified	33	3	36
Total interviews completed	25	3	28
Unable to complete interview because:			
Declined (too ill)	1	n/a	1
No response to phone messages or letters	2	n/a	2
No valid phone number and no response to letters	4	n/a	4
In CCR list, but would not be expected to be related to the period of excess*	1	n/a	1

*Moved to Oroville a few weeks prior to diagnosis

II. Update previous pancreatic cancer review

Question 1: Are there more cases of pancreatic cancer in the Oroville area during 2006 than would be expected?

The nine cases found in 2006 were fewer than the number of cases occurring in 2004 or 2005, but still greater than the expected number (six). However, if nine cases had occurred in 2006 without elevations in nearby years, this would not appear to be out of the ordinary.

III. Review cases to determine if unusual

2a. Are the cases unusual compared to the Oroville area cases from the previous four years?

A comparison of characteristics of cases from the period of excess of 2004-2006 to those from earlier years is shown in Table 3. The table includes the p-value for a test between groups to aid in evaluating differences; however, as the group numbers are relatively small, it was difficult to reach conventional levels of statistical significance.

Table 3: Comparison of pancreatic cancer cases from time period of excess with those in previous years.

Characteristic	Cases during period of excess 2004-2006 (n=33)	Cases 2000-2003 (n=28)	P-value for difference between periods
Female	18 (55%)	19 (68%)	p=0.6
White, Non-Hispanic	32 (97%)	25 (89%)	p=0.2
Age at Diagnosis <50 years	7 (21%)	2 (7%)	p=0.3
50-69	10 (30%)	10 (36%)	
≥70	16 (48%)	16 (57%)	
Socioeconomic status (SES) index			p=0.4
I	15 (46%)	14 (50%)	
II	8 (24%)	7 (25%)	
III	10 (30%)	7 (25%)	
IV-V	0 (0%)	0 (0%)	
Summary Stage at Diagnosis			p=0.4
Localized	6 (18%)	3 (11%)	
Regional by direct extension	6 (18%)	9 (32%)	
Regional by lymph nodes	2 (6%)	0 (0%)	
Regional by direct extension and lymph nodes	3 (9%)	0 (0%)	
Remote	14 (43%)	8 (28%)	
Unknown or not specified	2 (6%)	8 (28%)	
Exocrine Cancer	33 (100%)	28 (100%)	

Cases from the period of excess and from the earlier years were in most respects similar; sex, race and SES index remained consistent between the two time periods. One difference was that there were more cases under age 50 in 2004-2006 (21%) than in the four years prior (7%). Another difference was stage of cancer, with more of the cases in the time of excess having remote (metastatic) tumors. However, the stage of cancer was unknown for 28% of cases in the earlier years, so the true difference is unknown.

2b. Do the cases have accepted risk factors for pancreatic cancer in the typical frequencies?

Overview of descriptive information on typical pancreatic cancer risk factors

General health information for the patients is shown in Table 4A. We found over half of the cases had a BMI of 25 or more, which is above a healthy weight range. However, over their lifetime, only three (12 %) of the cases were described as mostly sedentary. Many (80%) were moderately or highly active, and around half of the cases regularly exercised.

The most frequently reported illness was pre-existing Type II diabetes, which was shared by ten cases. Family history of illness in biological relatives included 20 cases that had at least one family member with a history of cancer, and of those, five had three or more family members with a history of cancer. Four cases also had a family member who had pancreatic cancer. Eleven of the cases had a family member with Type II diabetes, and six of those had two or more family members with Type II diabetes.

Table 4A: Pancreatic cancer risk factors common among interviewed cases: physical and hereditary factors (n=25)

Body Mass Index	**Cases n (%)**
Obese: ≥30	5 (20%)
Overweight: 25-29.9	8 (32%)
Healthy: 18.5-24.9	11 (44%)
Underweight: ≤18.5	0 (0%)
Don't know	1 (4%)
Case has a history of:	
Diabetes (pre-existing)	10 (40%)
Hereditary pancreatitis	0 (0%)
Peptic ulcer	4 (16%)
Gastric surgery	1 (4%)
At least one family member with a history of:	
Cancer	20 (80%)
Pancreatic cancer	4 (16%)
Type II diabetes	11 (44%)
Stomach ulcer	5 (20%)
Breast cancer	6 (24%)

Table 4B summarizes dietary and environmental risk factors. Meat consumption data indicated about half of the cases ate beef or pork daily. Cured meats were consumed less frequently, and a majority of cases ate fruits and vegetables daily.

Thirty-two percent consumed alcohol daily, and 44% rarely or never consumed alcohol.

A majority of cases had a history of smoking cigarettes, cigars, or other products, and most of those had smoked for more than 20 years. Among nonsmokers, half were still exposed to smoke due to persons who regularly smoked in their environment.

Table 4B: Pancreatic cancer risk factors common among interviewed cases: diet and other environmental factors (n=25)

Diet – consumption	**n (%)**
Beef or pork	
Daily	14 (56%)
Weekly	9 (36%)
Monthly	2 (8%)
Rarely or never	0 (0%)
Cured or deli type meats	
Daily	3 (12%)
Weekly	12 (48%)
Monthly	6 (24%)
Rarely or never	4 (16%)
Fruits or vegetables	
Daily	18 (72%)
Weekly	6 (24%)
Monthly	0 (0%)
Rarely or never	1 (4%)
Alcohol	
Daily	8 (32%)
Weekly	5 (20%)
Monthly	1 (4%)
Rarely or never	11 (44%)
Environmental exposure	
Ever smoked cigarettes, cigars, or other	15 (60%)
Smokers: Years spent as a smoker:	
< 20 years	1 (4%)
20 – 29 years	4 (16%)
30 – 39 years	5 (20%)
> 40 years	5 (20%)

Table 4B continued:

Smokers: Number of cigarettes smoked per day: ≤ 20 cigarettes 20 – 39 cigarettes ≥ 40 cigarettes	 5 (20%) 7 (28%) 3 (12%)
Non-smokers: Had smokers in their environment once a week or more	5 (20%)

Comparison with other pancreatic cancer cases

Our comparison of the Oroville cases with large scientific studies found that the frequencies of pancreatic cancer risk factors among the Oroville cases to be in general similar (Table 5). The frequency of cigarette smoking among Oroville cases (60%) is within the range (58 - 69%) reported in other studies, as is the percentage of cases who are overweight. Having Type II diabetes before the onset of pancreatic cancer among Oroville cases (40%) is also within the range of other studies (11 - 60%). The wide range is probably due to the difficulty researchers have in determining whether the diabetes preceded the pancreatic cancer or was a consequence of it.[16]

The histories of other illnesses among the cases do not appear unusual for pancreatic cancer. Compared to a prevalence of 53% and 60% found in other studies,[17,18] the prevalence of cancer in a family member was somewhat higher in the Oroville group. However, different studies may define "family member" as more or less inclusive, and that may account for some of this variation. The Oroville cases also had a higher prevalence of individuals (16%) with other cases of pancreatic cancer among their family members, compared to other studies (5 – 10%).

Table 5: Frequencies of pancreatic cancer risk factors among Oroville cases compared to frequencies reported in other published studies of pancreatic cancer cases.

	Oroville cases	Falk 1988[17] (Louisiana)	Permert 1994[16] (Nebraska)	Ghadirian 2002[15] Quebec	Coss 2004[19] (Iowa)	Fryzek 2005[20] (Michigan)	Ko 2007[18*] (San Francisco Bay Area)
Ever smoked	60% (15)	67%		58%	69%	67%	69%
Prior diabetes	40% (10)		60%			28%	11%
Prior ulcer	16% (4)	12%					16%
Cancer in family member	80% (20)	53%					60%
Pancreatic cancer in family	16% (4)	6%		9%	5%	10%	7%
Overweight/ obese** (BMI ≥ 25)	52% (13)					61%	47%

*This study with Ko as the first author refers to Dr. Elizabeth Holly's research group at the University of California in San Francisco mentioned earlier.

** Body Mass Index (BMI) = 25 - 29.5 is overweight; BMI = 30 is obese.

2c. Do the cases share environmental, occupational, or other risk factor(s) to the extent that could plausibly account for the excess?

Overview of environmental factors

Seven cases consumed at least one type of locally produced meat or animal product. Eleven cases had eaten non-commercially caught fish. Seven of these ate fish from bodies of water in the Oroville region, three in other parts of northern California or elsewhere, and one did not specify a location. However, most people ate caught fish infrequently, and only one ate caught fish more than once a week, which would not suggest that the group would be receiving much exposure from fish consumption. Please see Appendix C for more detailed information about fish consumption.

When asked if cases had ever lived within a quarter mile of various sources of agricultural or industrial emissions (wood burning, rice burning, agricultural fields, or industrial facilities), typically two or three persons reported having lived near one of those. Nine cases also lived in areas where he or she could regularly smell or see airborne contaminants. Most people burned backyard trash and/or used wood burning fireplaces or stoves. Out of 15 cases who resided in Oroville during the 1987 Koppers fire, two recalled being evacuated from their homes, indicating they may have had some potential for exposure to the toxic fire.

Table 6: Risk factors specific to environment and residence (n=25)

Diet exposure – consumption of:	**Cases n (%)**
Locally raised meat product (total of any type)	7 (28%)
Chicken and/or eggs only	5 (20%)
Beef only	1 (4%)
Chicken, beef, and pork	1 (4%)
Non-commercially caught fish	11 (44%)
Exposures near residences	
Lived < ¼ mile from wood burning	2 (8%)
Lived < ¼ mile from (agricultural) rice burning	3 (12%)
Lived < ¼ mile from agricultural fields	3 (12%)
Lived < ¼ mile from industrial facilities	2 (8%)
Lived where s/he could regularly smell or see airborne contaminants, dust, or smoke	9 (36%)
Backyard trash or garbage burning	15 (60%)
Regular use of wood burning fireplace or stove	16 (64%)
Living in Oroville during 1987 Koppers fire	
Evacuated	2 (8%)
Not evacuated	13 (52%)

Exposure to contaminated water from Koppers

Of the 25 cases, no homes that used well water were located in the area of the PCP-contaminated Koppers groundwater plume. One person had worked at the wood treatment facility before it was acquired by the Koppers company, and so it would be possible that person may have used well water there. Two other worksites were located within a quarter of a mile of the plume boundary or the site, although the water source was not known. One other residence may have been near the site (the address is somewhat uncertain). We also checked addresses for the people we were unable to interview, and none were above the groundwater plume.

Overview of occupations

Of the 25 cases, one person reported having no occupational history. Among the rest, 84 occupations were reported over the course of their lives, although two occupations could not be classified due to lack of detail. The remaining 82 jobs were summarized into broader occupation categories (Table 7).

Table 7: Occupation groups reported for pancreatic cancer cases who had ever worked

Occupation Groups (2000 Census Occupation Codes)	**Jobs 'ever worked' (n)**
Management, Professional and Related (001-354)	7
Service (360-469)	24
Sales and Office (470-599)	13
Farming, Fishing and Forestry (600-619)	2
Construction and Extraction and Maintenance (620-769)	13
Production, Transportation and Material Moving (770-979)	23
Total no. of individual occupations	82*

*2 jobs were not able to be coded

Most jobs that people held throughout their lives were 'Service' occupations, such as food preparation and serving, healthcare support, and building and grounds maintenance. Slightly fewer occupations were classified as 'Production, Transportation, and Material Moving', such as production line workers and machine operators, bus drivers, and truck drivers. There were some 'Construction, Extraction, and Maintenance' occupations, as well as 'Sales and Office' occupations reported. The fewest number of jobs that people had were in 'Management, Professional and Related' and 'Farming, Fishing, and Forestry' occupations.

Overview of hobbies

In our review of non-work activities, we asked respondents to focus on activities that might have involved harmful chemical exposures, or that were somewhat unusual, so not all activities may have been reported. Most people reported at least one activity outside of work. Many people participated in outdoor activities, including: hiking, walking, and outdoor games (n=6); yard work and gardening (n=5); hunting and fishing (n=4); and other outdoor activities (n=5). Others – and some of the same persons – also engaged in indoor activities such as reading, sewing or cooking (n=8). Some reported activities involving woodwork/handyman (n=4); another area of activity involved working with metal and/or working on cars (n=5). Three persons did not report any hobbies.

Review of occupations and hobbies possibly associated with pancreatic cancer

The summary below reflects the work history of eight persons with exposure on the job only, five individuals with on the job and hobby exposure, and two with hobby exposure only (Table 8).

Table 8: Numbers of cases with exposures from occupations and hobbies with possible association with pancreatic cancer (n=25)

	Occupational exposure only	Hobby and occupational exposure	Hobby only	Total
Ionizing radiation	0	0	0	0
Metal exposure, primarily chromium	3	2	2	7
Asbestos	2	0	0	2
Polycyclic aromatic hydrocarbons (PAHs) and/or nitrosamines	5	0	0	5
Chlorinated solvents	8	0	0	8
Chlorinated pesticides	2	0	0	2
Non-chlorinated pesticides	2	1	1	4

The category with the most number of persons who reported some exposure was chlorinated solvents, followed by metal exposure, and then PAHs. An individual often had more than one exposure to a chemical that may be associated with pancreatic cancer. For instance, one individual had a work history that included probable exposure to metals, PAHs and nitrosamines, chlorinated solvents, chlorinated pesticides and non-chlorinated pesticides.

The person who had worked for the company that preceded Koppers would possibly have been exposed to particulates, PAHs, chlorinated pesticides, and fossil fuel combustion (although it is hard to know his exact exposure because his job was driving a truck and loading, not actual wood treatment).

Several respondents reported job-related activities that tended to have exposures thought to be associated with pancreatic cancer. These included working as mechanics or otherwise working closely with machinery and/or welding, and construction or road work. Sedentary occupations confer a low but consistent elevation of risk, and this risk factor was relevant for six persons in the group. On an individual basis, a few persons had higher than usual contact with specific exposures associated with pancreatic cancer, including one person who worked extensively with pesticides. No one had occupational ionizing radiation exposure, although one person had atypically high exposure from medical sources including possibly 10 CT scans and hundreds of x-rays. We also considered whether any occupation or exposure not previously identified in the scientific literature was held by a number of persons, but nothing stood out in this regard.

We also reviewed several other occupations, industries or exposures that have been mentioned in the literature as possibly being related to pancreatic cancer, although these are based on weaker or more contradictory evidence than those noted above. They include: electromagnetic fields; leather tanning; pulp and paper mills; butchers, fishmongers, brewery workers; biological research laboratory workers; textile workers; stonequarrying; woodworking; or other chemicals not mentioned above. None of the cases in the group fell in any of these categories, with the exception of several persons who were woodworkers, and possibly one person who worked as an electrician (may have had electromagnetic field exposure).

Individuals held jobs for varying periods of time and thus were exposed for different lengths of their total work history. For instance, one individual was exposed to chlorinated solvents for over 25 years. Another individual had limited metal exposure of one year at part-time job. We could not quantify exposure because we did not have detailed information about exposure levels.

There does not appear to be a particular exposure that may explain an excess of pancreatic cancer cases, although groups of persons had varied exposure to a number of chemicals possibly associated with pancreatic cancer. It may be that some of the different occupational and/or hobby exposures may have contributed to the excess. On the other hand, these types of exposures may be fairly typical for a group of people selected from anywhere in a modern society.

Risk factors and comparison of predicted prevalence among cases

In our analysis of the frequency which a risk factor would need to have among the cases in order to be a possible cause, we used guidelines described in the Methods section. We examined whether a given risk factor was shared by 13 or more of the 25 cases, for factors that would not exist or would be very rare outside Oroville (as this is half of our cases); and 17 or more for those factors that are more common (two-thirds of cases).

We applied these guidelines in consideration of potential exposures, listed below with the number of persons who have this characteristic:

- eating locally raised food (7);
- eating non-commercial fish (11);
- exposure to Koppers: contaminated drinking water from plume (1);
- exposure to Koppers: occupational (1);
- exposure to Koppers: smoke from fire (2);
- exposure to other smoke sources (varies);
- occupational exposures (especially chlorinated hydrocarbons and metals).

For most of these factors, fewer than half the cases experienced the exposure. Consuming locally raised food applied to seven persons, and most of the 11 persons who ate non-commercial fish did so infrequently, with only one more than once a week. Although exposure to Koppers from a variety of possible routes was a significant community concern, this group of cases did not present a link. One person had worked at the Koppers job site briefly prior to when it was acquired by Koppers (it was in the same business before), and may have drank the water. Two people were evacuated during the fire. For most of the other smoke sources, the number of persons reporting exposure varied from two to three. A larger number of cases (n=9) reported living at some time where there was some type of air pollution, although this was broadly interpreted and not specific to Oroville, e.g. positive responses included history such as living in Los Angeles. Some persons in the group had exposure to chlorinated hydrocarbons (n=8) or various metals (n=7).

The two risk factors that did have more than 50% reporting experiencing the factor were backyard trash burning (15 cases tended to do this generally once a year in the fall) and using a wood-burning stove (16 cases). However, it seems most likely that these were very common activities in the past for rural areas. Even though these factors were reported by more than our guideline number of 13, they did not exceed the guideline number of 17 for more common activities.

Summary of characteristics and risk of additional cases

As noted earlier, in addition to the cases identified in the Registry, several other persons contacted us with information about a family member who had pancreatic cancer. Two of these cases were diagnosed in the time period of excess and had previously lived in Oroville, but were no longer living there at the time of diagnosis. Another was diagnosed shortly after the time of the period of excess. These three persons seemed generally similar to the rest of the cases in the group. All were over 70 years of age at time of diagnosis. They had a variety of known risk factors: all had at least one family member who had cancer, and one had a family member with diabetes. One person had pre-existing diabetes, and the other two may have had diabetes or were bordering on this condition. Two were overweight; two were smokers, and one had chewed tobacco (although not for a long period of time). None worked for Koppers, and only one resided in Oroville at the time of the 1987 fire and not in an area affected by evacuation.

Another two persons contacted us regarding cases that were not diagnosed during the excess period. One was diagnosed after and one several years before the period of excess, during years in which no excess occurred. One had lived in Oroville at several time periods in the past, and the other's residence there was the 10 years immediately preceding the person's diagnosis. One person may have resided in Oroville during the time of the fire, although it is not known if the person was evacuated. Several risk factors were present, such as smoking and family history of pancreatic cancer. Neither had used well water in Oroville, and both had service occupations with no unusual exposures at work or outside of work

Comparison of characteristics of interviewed cases vs. not interviewed cases

As we did not obtain an interview for 8 of the 33 cases, we reviewed the routinely collected Cancer Registry data to compare the demographics and cancer types among those interviewed and not (Table 9).

Cases not interviewed were somewhat more likely to be over 70 years old and in the lowest SES level. Whether there are environmental factors that would be more likely to affect this group compared to the group that we interviewed is unknown.

Table 9: Comparison of cases interviewed with those not interviewed.

Characteristic	Interviewed n=25		Not Interviewed n=8		P-value
Female	13	(52%)	5	(63%)	0.6
White, Non-Hispanic	25	(100%)	7	(88%)	0.2
Age					
<50	5	(20%)	2	(25%)	0.4
50-69	9	(36%)	1	(12%)	
≥ 70	11	(44%)	5	(63%)	
SES Index (Yost scale)					
I	10	(40%)	5	(63%)	0.5
II	7	(28%)	1	(12%)	
III	8	(32%)	2	(25%)	
IV-V	0	(0%)	0	(0%)	
Summary Stage at Diagnosis					
Localized	5	(20%)	1	(13%)	0.4
Regional by direct extension	3	(12%)	3	(37%)	
Regional by lymph nodes	2	(8%)	0	(0%)	
Regional by direct extension and lymph nodes	3	(12%)	0	(0%)	
Remote	11	(44%)	3	(37%)	
Unknown or not specified	1	(4%)	1	(13%)	
Exocrine Cancer	25	(100%)	8	(100%)	
Occupation					
Not assigned	25	(100%)	8	(100%)	

DISCUSSION AND SUMMARY

We conducted an active and comprehensive investigation to gather in-depth information on cases' background and risk factors that is not routinely collected by the Registry, and in particular to search for any unusual environmental factors that may be relevant to the Oroville area.

Persons in the group tended to work in service, construction, production and transportation areas. Many possessed technical skills such as mechanics or carpenters, and at times their skill set was also applied to extensive hobbies. Most people led fairly active lives, at work or outside work, and many participated in outdoor activities.

Generally, we found that the demographic and pancreatic risk factor profile for the group appeared consistent with other groups of pancreatic cancer patients.

One exception to this general conclusion was that during the period of excess, there were a few more persons who were younger than what was seen among the cases in the previous few years in the Oroville area. At this time, we do not associate any particular significance with this. However, it is worthwhile noting as future cancer research may inform the finding.

We explored a number of possible environmental and occupational exposures that were originally mentioned as concerns, as well as sought to identify any that the persons we interviewed may have been aware of that we were not. Because of concern raised about exposure through eating locally caught fish that may have had high levels of contaminants, we included this topic in the interviews, although this did not turn out to be a likely cause of the excess.

One focus of our inquiry was the former Koppers wood treatment facility. If we had found that a large number of cases had a connection to the facility, this might suggest an exposure that contributed to the excess, but our findings that no one had lived in a house where well water affected by the plume was used, and only one person had worked at that site, did not suggest a connection. Our investigation of the Koppers fire similarly did not suggest that it was likely to have been responsible for the excess, as only two lived in an area that was evacuated. It is also helpful to realize that, in general, it usually takes exposure over a long period of time to cause cancer, rather than a relatively short-lived, one-time event.

The likelihood that exposures to fire causes pancreatic cancer is informed by a meta-analysis of a number of studies of cancer in firefighters, where the authors concluded that pancreatic cancer was probably unlikely to be caused by firefighting.[21] Also, studies of a town in Italy where an explosion of a chemical plant in 1976 released amounts of dioxin much greater than any other known community exposure found incidence and mortality for pancreatic cancer have not been elevated since then.[22]

In addition to the investigation of environmental hazards, we considered potential occupational sources of exposure. Although our review did not find a specific occupation that would have plausibly accounted for the excess, we did find several occupations/hobbies represented among the cases that have been found in scientific studies to be associated with pancreatic cancer, such as those involving work with metals, solvents, and pesticides.

We also asked everyone we spoke with to carefully consider whether there was any other exposure or situation that they could recall that might have conferred exposure or have been unusual in any way. This also did not uncover any previously unidentified factor in common among the group.

That this investigation did not identify a common risk factor among the cases is not atypical; in fact, specific causes for the vast majority of community cancer clusters are rarely found.[23,24] Most experts on cancers and cancer "clusters" believe that clusters appear in neighborhoods far more often than most people would realize.[25] If the entire state is considered, given that there are thousands of communities, there is a very good probability that some will have higher than normal cancer rates by chance.

Furthermore, there are barriers that exist that would make it difficult to recognize an environmentally caused disease excess. These include: the long latency period for cancers; the fact that the same type of cancer can be produced from different exposures; and the inability of science to detect specific exposures in individual cases of cancer. Also, in an investigation such as this which relies on information gathered from interviews, patients or their next-of-kin may not fully recall a 20 or 50 year work history and may not know about past exposures.

We can list several possible explanations for the observed 80% excess of pancreatic cancer in Oroville. Any or all of these may have contributed at least in some part to the excess.

1. The occurrence of an 80% excess in pancreatic cancers was by chance. As the number of cases of cancer that appear year by year can fluctuate for reasons unrelated to environmental exposures (such as personal mobility, varying times of diagnoses), it may be that the additional cases observed in 2004 and 2005 were chance occurrences that would be unlikely to be repeated. We note that the nine cases in 2006 fall within the expected range of statistical fluctuation.

2. The expected number of cancer cases, which forms the basis for assessing whether the community occurrence is unusual, is based on population estimates of the community, including the size of the population and the proportion of older people who have the highest rate of pancreatic cancer. Population counts from the U.S. Census are made once a decade, and in between the census years the population size is only estimated. Although these estimates attempt to account for change in the population, if they are incorrect for any reason, such as due to population growth, decline, or aging, they may lead to an incorrect impression of whether the number of cases seen is out of line.

3. Greater than expected prevalences in the community may exist for several risk factors for pancreatic cancer, such as smoking, overweight, diabetes or diet that would increase the community-wide rate but not make the cases appear unusual.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, we performed an extensive field investigation and data review and found no common factor among the cases that could plausibly account for an excess of pancreatic cancers. Many cases shared a known risk factor for pancreatic cancer (such as smoking, being overweight, having diabetes, or a family history of pancreatic cancer), and some worked at specific occupations that may be linked to pancreatic cancer (such as mechanic, welding, working with pesticides), but no widespread exposure or unusual Oroville circumstances appeared responsible for the excess.

We recommend continued monitoring of the occurrence of pancreatic cancer for the next few years to determine if the number of cases returns to within the expected range, as is suggested by the decline in more recent data, or whether an excess persists.

ADDENDUM

Since the time the investigation was conducted, an additional case was reported that had been diagnosed in 2006, so the total for year 2006 is 10 cases rather than 9.

Appendix A: Pancreatic Cancer Information and Resources

1. How pancreatic cancer is diagnosed

If pancreatic cancer is suspected, the doctor does a complete physical exam and asks about the patient's personal and family medical history. In addition to checking general signs of health (temperature, pulse, blood pressure, and so on), the doctor usually orders blood, urine, and stool tests. The doctor may also ask for specialized tests of the upper gastrointestinal system, or certain other tests that make pictures of the inside of the body, called imaging tests.

Currently, there are no blood tests or other tests that can easily detect this cancer early in people without symptoms. Levels of certain tumor markers may be higher than normal in people with pancreatic cancer, but the cancer is usually advanced by the time the levels become high.

2. How to reduce risk of pancreatic cancer (recommendations from the Mayo Clinic)

Although there's no proven way to prevent pancreatic cancer, you can take steps to reduce your risk, including:

- Quit smoking. If you smoke, quit. Talk to your doctor about ways to help you quit, including support groups, medications and nicotine replacement therapy. If you don't smoke, don't start.

- Maintain a healthy weight. Being overweight increases your risk of pancreatic cancer. If you need to lose weight, aim for a slow, steady weight loss — 1 or 2 pounds (0.5 or 1 kilogram) a week. Combine daily exercise with a plant-focused diet with smaller portions to help you lose weight.

- Exercise regularly. Aim for 30 minutes of exercise on most days. If you're not used to exercising, start out slowly and work up to your goal.

- Eat a healthy diet. A diet full of colorful fruits and vegetables and whole grains is good for you, and may help reduce your risk of cancer.

Note: The above recommendations are from the Mayo Clinic Website: http://www.mayoclinic.com/health/pancreatic-cancer/DS00357/DSECTION=prevention.

3. Other resources outside the health department:

American Cancer Society:

ACS is a national non-profit organization which provides information for the public, cancer prevention and other community programs, research support, and advocacy on cancer issues.

Phone: 1-800-ACS-2345
Internet address:
http://www.cancer.org/docroot/CRI/content/CRI_2_2_2X_What_causes_pancreatic_cancer_Can_it_be_prevented_34.asp?sitearea=06/08/2007

Pancreatic Cancer Action Network*:*

From their website: “This is a nationwide network of people dedicated to working together to advance research, support patients, and create hope for those afflicted with pancreatic cancer.”

Phone: 877-272-6226

Internet address: http://www.pancan.org/

Pancreatica*:*

Pancreatica is a non-profit organization with a free counseling line for information on pancreatic cancer, provided in collaboration with the University of Colorado Cancer Center.

Phone: 1-800-525-3777. The website says: “Call 1-800-525-3777 for free counseling on our Cancer Information and Counseling Line (CICL).

Internet address: http://www.pancreatica.org/

“The purpose of this site is to serve as a worldwide gathering point on the Internet for the latest news and disinterested information in regard to clinical trials and other responsible medical care in the treatment of pancreatic cancer. Additionally, our aim is to present impartial knowledge about pancreatic cancer where interested parties can sort through a large amount of information efficiently in order to give a sense of the range of existing treatment options, to aid patient/doctor partnerships, and thus to help optimize personal treatment strategies.”

Appendix B: Predicted Prevalence of a Risk Factor

This appendix describes the derivation of formulae used to relate the strength of a risk factor (the relative risk), the prevalence of exposure in the index and referent communities, and the incidence rate ratio (SIR) of the index community. The incidence rate in the index community under study is proportional to the relative risk of exposure combined with fraction of the population exposed. Let RR be the relative risk from exposure. The overall community incidence is made up of two parts: $P_1(RR)$ is the part due to exposure in the proportion of the index community exposed (P_1), and $(1-P_1)(1)$ is the part due to the complementary proportion of the population unexposed (among whom by definition RR = 1). The rate in the index community is therefore proportional to $P_1(RR) + (1-P_1)$. Similarly, in a reference area used to generate the expected number of cases, where P_0 is the proportion exposed, the rate is proportional to $P_0(RR) + (1-P_0)$.

The observed-to-expected ratio of cases in the index community relative to the reference area, also known as the standardized incidence ratio or SIR, is the ratio of the two rates above:

$$SIR = [P_1(RR) + (1-P_1)] / [P_0(RR) + (1-P_0)]$$

If we assume values for P_0 and RR, we can solve for P_1, the proportion of the index community that is exposed:

$$P_1 = [SIR(P_0(RR-1)+1) - 1] / (RR-1)$$

This formula can be helpful in judging whether certain combinations of risk factors and exposure frequencies are plausible. In the Oroville experience, where the SIR = 33/18 = 1.8 and most known risk factors for pancreatic cancer have RRs no more than 2 or 3, a factor responsible for this SIR would have to expose at least 40% or 50% of the Oroville populace if the exposure were unique to Oroville ($P_0 = 0$), or well above 50% if the exposure were present in 10 to 20% of the reference population.

Imagine such a risk factor did exist with sufficient prevalence and of sufficient strength to cause the observed SIR. If we were to examine the cases that occurred in the community, what proportion of the cases would have to share that risk factor? The total number of cases in the community (arising from both the exposed and unexposed fractions) is $N*R*P_1*RR + N*R*(1-P_1)$, where N = the size of the population, R the background or expected rate of the disease, P_1 the proportion of the population exposed, and RR the relative risk increase produced by the exposure.

The number of cases arising only from the exposed is the first part of the above equation: $N*R*P_1*RR$. Then P_c, the proportion of cases with the exposure, is $[N*R*P_1*RR] / [N*R*P_1*RR + N*R*(1-P_1)]$, which reduces to:

$P_c = [P_1(RR)] / [P_1(RR) + (1-P_1)]$

Using the equations for various plausible combinations of P_0 and RR, we can calculate the proportion of the cases that would have been exposed had that exposure been responsible for the observed SIR.

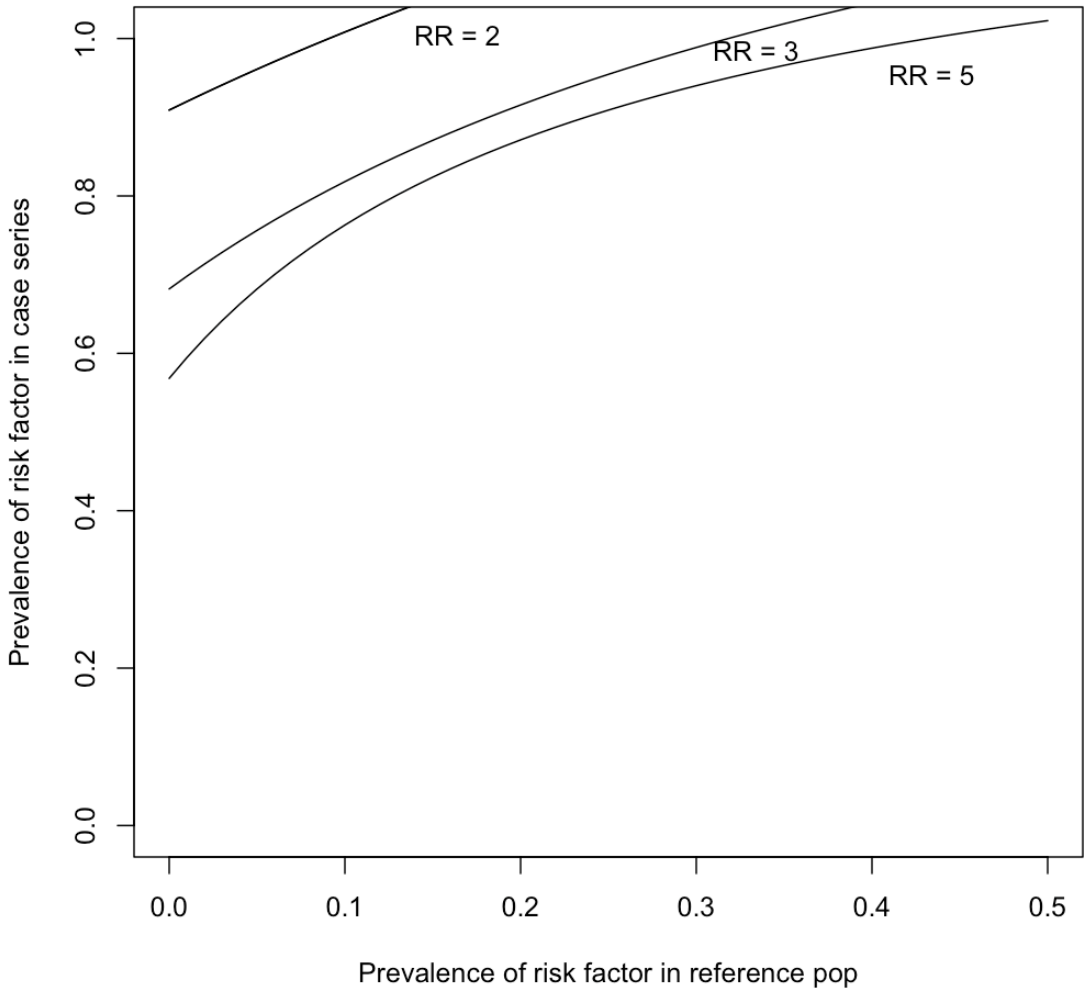
Figure A-1 shows the proportion of cases who would have to share risk factors, with RR = 2, 3, and 5, in order for that factor to account for the observed Oroville community-wide excess number of cases. For risk factors that are not present or very rarely present outside Oroville (P_0 near zero), at least 50% of Oroville cases would have to share that exposure. For more common risk factors, two-thirds or more of the cases would have to share that factor. A risk factor seen among 10 or 20% of the cases is simply not widespread enough to account for a near doubling of the community cancer rate. Thus we can estimate, in advance of analyzing the case series, the frequency a risk factor would need to have among the cases in order to be a possible cause.

In this situation, the exposure would have to be nonexistent in the reference area and ubiquitous in the index community in order to double the entire index community's incidence. If another putative risk factor were present in 20% of the reference population, and exposure to it increased the disease risk three-fold (RR = 3), it would have to be exposing 90% of the individuals in the index community in order to account for a doubling of the community-wide rate. This information can help us judge whether certain combinations of risk factors and exposure frequencies are plausible.

We can take these calculations a step further: if a single exposure in Oroville were responsible for the increased cancer rate, how many of the cases would be expected to have this exposure? Clearly, an exposure seen in only one or two cases cannot be sufficient to account for a near doubling of the community-wide rate.

With this approach, we can calculate the proportion of cases that would show the exposure to a risk factor if that factor were responsible for the 1.8-fold increased rate of cancer.

Therefore, a community factor, if one exists, that could explain the excess would have to be fairly common in Oroville, and present in well over half the cases. We can use this as a guide to help us assess different scenarios of possible exposure risk factors from the case interviews.


RR = 2
RR = 3
RR = 5
Prevalence of risk factor in case series
Prevalence of risk factor in reference pop
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.1
0.2
0.3
0.4
0.5

Appendix C. Information on fish consumption and contamination

Prior to and apart from this investigation, EHIB has been involved in assessing contamination in fish and bodies of water in various locations in California, including the Oroville area. We can provide some background information on what is known about contamination in the area generally. Historic gold and mercury mining have left a legacy of fish contamination in the Sacramento-San Joaquin Delta watershed, an area that includes the Feather River watershed.[26,27] Mercury was used in the gold mining process, and as a result, elevated levels of mercury in fish can be found throughout this region.

Fish consumption guidelines focus on women because the main concern is exposure to mercury, which can affect brain development and the nervous system. State advisories due to mercury contamination in fish have been issued for the lower Feather River (http://www.oehha.ca.gov/fish/so_cal/Featherdraft081006.html) and several reservoirs and rivers in the Feather River watershed (http://www.oehha.ca.gov/fish/so_cal/nosierra.html). Fish monitoring for mercury and some organic contaminants has been conducted at Lake Oroville by the Department of Water Resources[28,29]; however, an advisory has not yet been issued based on this information. All state advisories can be found at http://www.oehha.ca.gov/fish/so_cal/index.html. Monitoring of all water bodies in the state is incomplete, and little is known about chemicals other than mercury. The absence of an advisory is not an indication that the fish are safe to eat.

The U.S. Environmental Protection Agency (U.S. EPA) and the Food and Drug Administration (FDA) have issued a national advisory which recommends that high risk populations limit their intake of sport-caught fish. High risk groups include pregnant and nursing women, women who may become pregnant, and young children. In the absence of a state or local advisory, these groups should limit sport fish consumption to no more than one meal (6 ounces cooked weight) per week. U.S. EPA and FDA also recommend that high risk groups limit their intake of commercial fish (fish purchased from stores or restaurants). More information can be found at: http://www.epa.gov/waterscience/fish/advice/.

Although mercury is primarily a concern due to its potential harmful effects on neurodevelopment, it may be carcinogenic as well. U.S. EPA considers two forms of mercury, mercuric chloride and methyl mercury, to be possible human carcinogens (http://www.atsdr.cdc.gov/tfacts46.html#bookmark06). The State of California under Proposition 65 considers methyl mercury a carcinogen (http://www.scorecard.org/chemical-profiles/html/mercury.html).

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