Cancer Cluster Investigation within the Mission Memorial Hospital Laboratory

Final Report

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Executive Summary

This investigation was conducted in response to concerns expressed by employees of the Mission Memorial Hospital (MMH) Laboratory that they were experiencing a high incidence of cancer. The investigation resulted in an initial report prepared by the Occupational Health & Safety Agency for Healthcare in BC (OHSAH) and released for comment in March, 2004 (Attachments 2 & 3). The associated presentation is included as Attachment 4. In addition, Attachments 5, 6 and 7 are supportive documents from the initial investigation. Subsequently a new breast cancer case was identified and errors in staffing levels were corrected. A re-analysis of the breast cancer incidence rate was completed in April, 2005 (Attachments 8 & 9) and a revised Draft Report was released in September, 2005. The revised Draft Report still did not address all of the concerns raised by the MMH Laboratory employees and resulted in a set of critical questions being posed which were presented to the Fraser Health Authority (FH) and OHSAH in November of 2005 (Attachment 10). The responses to these questions for which OHSAH was responsible were sent to FH and the Health Sciences Association (HSA) in January, 2006 (Attachment 11) and were presented at MMH on February 8th, 2006 to representatives of FH, HSA, the BC Nurses' Union (BCNU) and the Hospital Employees' Union (HEU). Some of the questions posed by the Laboratory employees were responded to by FH and are included as a separate document. This Final Report is therefore a compilation of the investigation of cancer incidence at the MMH Laboratory and the results of an extensive consultation process with the employer, labour representatives, and the individuals involved.

The results of this investigation are presented in three parts: a comprehensive review of the literature, an epidemiologic cluster analysis, and an occupational exposure investigation. The investigation procedures followed the established guidelines by the BC Cancer Agency (BCCA) for cancer cluster investigations[1]. These guidelines are in keeping with international approaches[2].

In summary, 64 individuals were identified as having worked in the laboratory between January 1, 1970 and December 7, 2004. Information on health status and diagnosis of cancer were obtained through personal interviews with employees. One person was diagnosed with cancer

[1] Guidelines for the Investigation of Cancer Clusters in BC. BC Cancer Agency, Cancer Control Research, November 1998.
[2] Guidelines for Investigating Clusters of Health Events. US CDC, July 27, 1990.

prior to working in the MMH laboratory and was excluded from the analysis. Of the remaining employees, ten employees reported a cancer diagnosis, of which seven were breast cancer. A total of 974 person-years of observation were available for the data analysis after excluding one subject because of diagnosis of cancer prior to start of employment. Based on the age and calendar-year adjusted rates for the BC population, the expected number of breast cancer cases in the women was 0.8 and the expected number of all cancers for all employees was 2.3. The Standard Incidence Ratios (SIR), which is the observed number of cases divided by the expected number, was found to be 8.4 for breast cancer among women at the MMH Laboratory, and 4.7 for all cancers among both men and women at the lab. In other words, the risk for breast cancer was over 8 times the expected rate; and the rate of all cancers was over 4 times the expected rate. The 95 percent confidence intervals indicate that both findings were significant. It can be concluded that the perception of the laboratory workers that they were experiencing an excess in cancer was confirmed – i.e. this is truly an observed cancer cluster.

The risk of developing breast cancer was also analyzed by the age at first employment at the MMH Laboratory, the subjects' length of time at work prior to diagnosis and by their job title. The most important result was that no association was found between breast cancer risk and either the age of first employment or the duration of exposure. However, there was a non-significant increase in risk by job title with 'technician' being at greater risk than the grouping 'aid, clerk, or ECG technician'.

A walk-through survey of the laboratory in its present state did not identify any potentially hazardous exposures for which control measures are not in place. Review of indoor air quality records and chemical assessment of carcinogens in the workplace also did not show any obvious and extreme exposures in the past (based on current scientific literature), which could be related to the increase in risk. Assessment of radiation exposure in the laboratory was also found to be at typical natural background and would not contribute measurably to increased cancer risk. Thus, while it can not be ruled out that workplace factors played some role in the complicated process of carcinogenesis that led to this tragic outcome for laboratory workers and their families, the exact relationship between workplace exposures and the cancers that resulted remains elusive.

The evidence collected to date does not allow us to reach scientific conclusions to support the association between work-related exposures and breast cancer in this cluster. However, this

report has confirmed that this is indeed a statistical significant cluster. This usually points to the need to follow up with an etiological study with the required statistical power to investigate for this association while controlling for other non-work related exposures. Prior to embarking on such a study however, there is a need to establish an etiological hypothesis based on scientific evidence that provides proposed mechanism(s) for breast cancer causation. Our review of the literature was unable to establish the basis for such a hypothesis, as we did not find any scientific evidence for the plausibility of a laboratory work-related etiological hypothesis regarding breast cancer. While dioxins from the incinerator stack emissions have been implicated with other cancers, these did not include breast cancers; despite the potential exposure of MMH Laboratory workers to these emissions. Moreover, the number of people who worked in the Mission Hospital Laboratory is not sufficiently large to provide an adequate sample size for an etiological investigation.

Thus, it is recommended that this specific cancer cluster investigation be closed and the analysis updated in five years. If new evidence emerges to support a disease causation hypothesis for laboratory work-related breast cancer, and a larger study with an adequate sample size can be designed, then this subject could be investigated further at that time.

It is important to understand that human beings are exposed to carcinogens in almost all environments, at home, at work, and even walking in the sunshine. Every effort should be made, in this and all workplaces, to ensure that the workplace remains as safe and free of carcinogenic exposures as possible, and that the workforce is able to pursue safe and healthy choices in all aspects of their lives.

Forward

This report is the culmination of work conducted by numerous individuals, either on staff at OHSAH, serving as an OHSAH consultant or as a UBC trainee on rotation at OHSAH. Key personnel include the authors, Phil Bigelow, Shicheng Yu, Trevor Corneil, Victor Omelchenko, Malcolm Steinberg, and George Astrakianakis. We acknowledge the strong support and assistance of the BC Cancer Agency (Drs Nhu Le, Greg Hislop, and Malcolm Hayes), the School of Occupational and Environmental Hygiene at the University of British Columbia (Dr. Paul Demers), the Fraser Health Authority (Mr. Dave Keen and Ms. Rosemary Nemanishen), and the Health Sciences Association (Mr. Marty Lovick and Ms. Bev Banfield).

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Table of Contents

- *Attachment 11A:* OHSAH responses to critical questions (January 9th, 2006)
- *Attachment(Separate Document):* FH responses to critical questions

Introduction

The Occupational Health and Safety Agency for Healthcare (OHSAH) was invited by the Fraser Health Authority (FHA) to investigate concerns of a greater than expected number of cancer cases in the Mission Memorial Hospital (MMH) Laboratory. In addition to the seemingly high total number of cancer cases, a large proportion were the same type (breast cancer) thus further highlighting the need for an investigation. Occupational health professionals from FHA had completed some exploratory work on the project but felt they needed the help of outside experts to resolve the issues. OHSAH contacted the Health Sciences Association (HSA), the union representing the lab workers, and ascertained that they were in agreement with OHSAH taking the task and requested us to proceed. The resultant cancer cluster investigation conducted by OHSAH is the focus of this report.

A cancer cluster is the observation of a higher than usual occurrence of cases of the same type of cancer, or all cancers, within a geographic location over a specified period of time. The purpose of a cancer cluster investigation is to determine if the observed number of cases is statistically higher than expected. If the observed incidence rate is higher, then the investigation should review if the subjects involved were exposed to a potential causative agent that can be identified, and if the investigation should progress to a more systematic review of exposure and incidence. In BC, these investigations are conducted following guidelines recommended by the BC Cancer Agency in keeping with protocol used in other jurisdictions across North America [1-4].

Prior to the investigation, an explanatory meeting was held at MMH to discuss the incidence of cancer at MMH Laboratory and the protocol for the investigation. Details of the protocol used during the investigation are provided below.

Methods

The specific aim of this study was to provide a determination if an excess in the number of cancer cases had occurred in the MMH Laboratory and to provide information regarding occupational exposures and the possibility that a work-related factor was involved. More importantly, the goal was to review current workplace conditions and occupational exposures to confirm they are not likely to result in an increased risk of cancer for employees.

The BC Cancer Agency has adopted standard protocols for investigating clusters [5]. The methods used in our study followed these standard procedures and included determining if an excess number of cancers were reported, a literature review on the risk factors for the specific cancer types, assessing the potential for occupational exposures to potentially carcinogenic physical agents or substances, and determining the feasibility of further epidemiology studies. Our study was divided into three components as listed below.

Review of Literature

The investigation of a potential cancer cluster is complex. This report includes a review of the literature regarding risk factors for breast cancer, exposures in laboratories, and epidemiology of cancer clusters. The summary of the literature review is presented first. It provides background for interpreting the findings from both the epidemiologic analysis and the field surveys. The review of the epidemiologic literature of breast cancer highlights the multi-factorial nature of disease causation and the difficulties in determining the role of environmental and occupational exposures as causal factors. Finally, the findings of the statistical analysis are provided and discussed in relation to findings from other studies.

Analysis of Cancer Incidence Data: Epidemiology and Statistics

Employees who worked in the MMH Laboratory from January 1970 to December 2004 were identified using records from the Human Resources Department of MMH. A total of 64 individuals were identified and the following information was collected from their records: date of birth, dates of employment at the lab, job title, full or part time employment status, gender, and other details pertaining to work at the lab and hospital. A health professional (Registered Nurse) from Fraser Health attempted to contact all individuals (in person or by telephone) to gather information on whether or not they had a diagnosis of cancer of any type. For individuals who reported a cancer diagnosis, information on the diagnosis date, type and site of cancer was obtained. One employee reported a diagnosis of cancer prior to beginning work at the MMH Laboratory and was excluded from the analysis. Data for all individuals, without personal identifiers, were entered into a spreadsheet and provided to OHSAH.

The statistical analysis was conducted two ways. In one, the person-years of observation were defined as being from the start date of employment at MMH Laboratory to the end date of

employment. In the second analysis, the person-years of observation were defined as the time between the employee start date and the end of the follow up period (August 2004). In this report the latter analysis is provided, as it is the most appropriate for the study design that was used.[3]

Since a large proportion of the cases were classified as breast cancers, statistical analyses were conducted using rates of breast and total cancers obtained from the BC Cancer Agency. Rates for breast and total cancers for each year from 1970 to 2004, grouped by 5-year age intervals, were used to calculate the expected number of cases in the study group. The expected number of cases is the number of cases expected in the Laboratory if the rate was the same as the rate in BC adjusted for age and calendar year. The expected number of cases was computed by multiplying the population (person-years of observation) within each specific age range and year by the rate of breast or total cancers for the same age interval and year. The results of these computations were summed across all the age and year categories to get the total number of expected cases. Computations and statistical analyses were conducted using Excel and SPSS software.

The observed number of cases was divided by the expected number of breast cancer and total cancer cases to determine the Standard Incidence Ratios (SIR). A SIR exceeding 1.0 indicates the observed number is higher than expected. Confidence intervals are used to assess variation in the SIR and 95% Poisson confidence intervals were calculated using the procedure suggested by Breslow [6]. To investigate the relationship of occupational factors on the rate of developing breast cancer, a Cox proportional hazard model was developed that included independent variables for job title, job status (full or part time) and age at start of employment at the laboratory.

Initially, the epidemiological and statistical analysis of the cancer incidence data was conducted for 57 individuals and the report that has been produced in March 2004 was based on this number of employees (Attachments 2 and 3). However, an update for the report was performed in March 2005 since a new case of breast cancer in the workforce came to light, and along with it, a request to redo the analysis. This new report was based on the updated number of 63 eligible employees (57 of whom were female). This change in the number of cases and the employee

[3] In many occupational cohort studies, when subjects leave employment, their health status at that time is known and their end date of employment is used in the computation of person-years of observation. In this study, we contacted all study subjects from August to November, 2003 to determine their health status.

numbers affected both numerator and the denominator of the incidence calculations (Attachment 8).

Field Investigations: Possible Exposures to Potentially Carcinogenic Substances or Physical Agents

Prior to this investigation, work had been conducted by occupational health professionals at Fraser Health to determine the adequacy of procedures to control exposures to chemicals in the laboratory and to ensure exposures did not exceed government or consensus standards. Investigations also focused on potential sources of chemical exposures resulting from work tasks that are typically performed by laboratory personnel. Additionally, studies that involved reviewing past renovations of the laboratory in hopes of identifying unusual sources of indoor air contaminants were performed.

In August of 2003, as part of the investigation, a walk-through survey of the laboratory was completed. Typical work procedures were reviewed to assess the potential for exposures to hazardous agents. Employees in the laboratory provided information on historical procedures as well as an indication of the general levels of exposure to air contaminants.

In 2004, an environmental review was conducted and included: chemical agent assessments (specifically assessment of possible exposure for known carcinogens), physical agent assessment (radiation assessment) and indoor air quality assessment.

Literature Review

Breast Cancer Epidemiology

Breast cancer is one of the most common female cancers in North America, the second most common cause of cancer death in women (after lung cancer), and the main cause of death in women ages 45 to 55. Canada has one of the highest rates of breast cancer. The incidence and the age standardized rate in 1995 exceeded 225 per 100,000 women aged 40 and over [7,8]. In Canada, breast cancer accounts for over 30% of new cancer cases per year [9]. In 2005, an estimated 21,600 women will be diagnosed with breast cancer and 5,300 will die of it. According to the Canadian Cancer Society, 415 Canadian women will be diagnosed with breast cancer every week and, on average, 102 Canadian women will die of breast cancer every week [10]. The

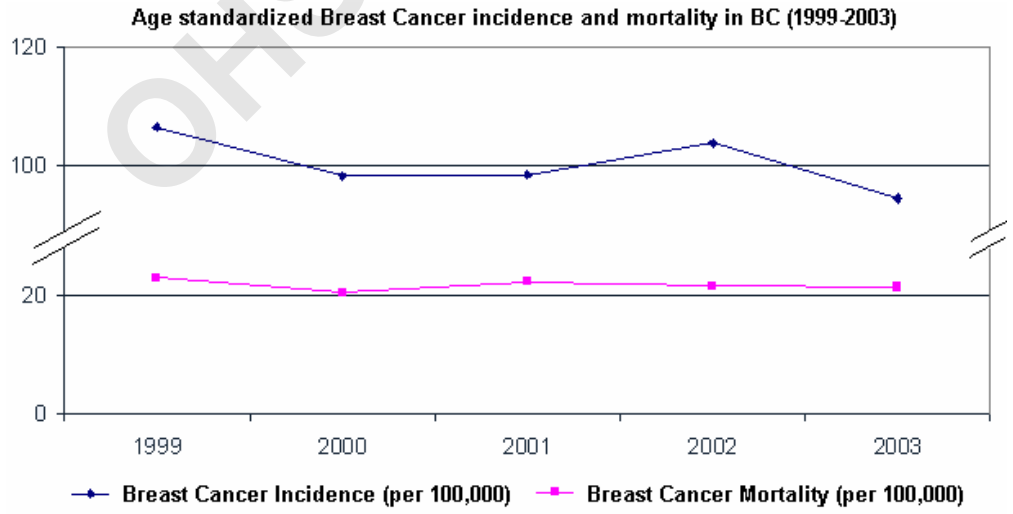
province of British Columbia is not an exception. Every year in British Columbia, breast cancer is diagnosed in approximately 2,500 women and causes more than 500 deaths, second only to tobacco-induced lung cancer as the cause of cancer deaths amongst women [11]. In 2003, among all cancers, the breast cancer incidence rate for all age groups was 118.1 per 100,000 which is twice as high as the incidence of lung cancer (second leading cancer) and the mortality rate was the second highest (29.2 per 100,000). (Figure 1).

Figure 1. Cancer incidence and mortality in 2003 in British Columbia. Source: BCCA Cancer Statistics 2003

INCIDENCE		MORTALITY	
Breast	118.1	Lung	44.2
Lung	54.4	Breast	29.2
Colon/rectum	51.6	Colon/rectum	16.7
Uterus	23.9	Ovary	11.7
Lymphoma	18.1	Pancreas	11.2
Melanoma	13.7	Lymphoma	7.4
Ovary	12.8	Leukemia	5.3
Pancreas	11.5	Uterus	3.9
Leukemia	8.2	Bladder	2.9
Mouth/Pharynx	6.0	Melanoma	2.7
Bladder	5.7	Mouth/Pharynx	1.8

The incidence rate, however, in 2003 was found to be the lowest in the last five years; the mortality rate did not change (Figure 2).

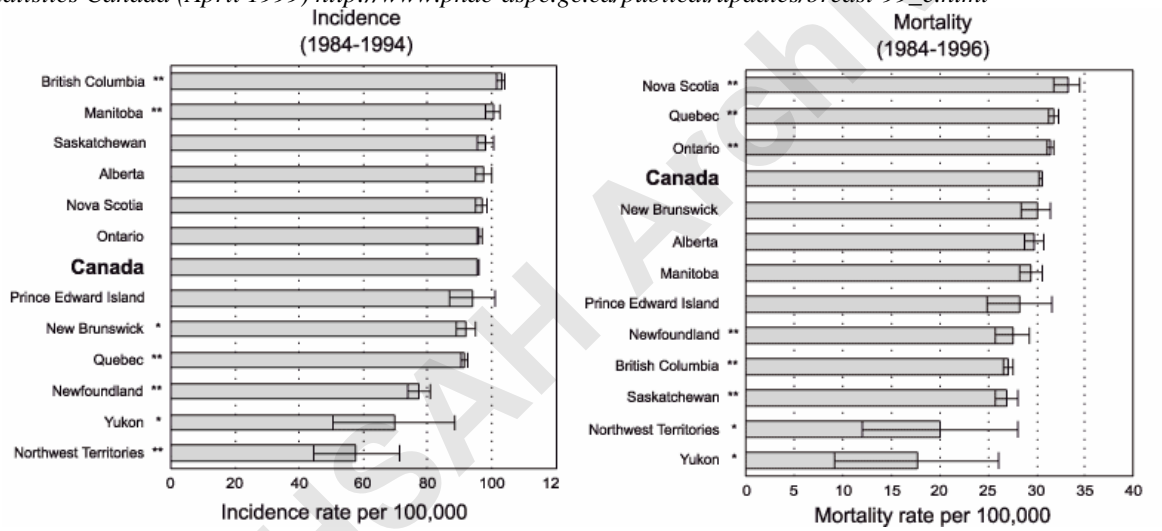
Figure 2.



The majority of breast cancer cases can be explained by known risk factors, such as age at menarche, first live birth, and menopause, proliferate-breast disease, and correlated factors such as socioeconomic situation. An additional 10 percent of breast cancers are associated with a positive family history [9].

Comparative analysis of the incidence and mortality rates of British Columbia versus other Canadian provinces, conducted in 1998, show that in 1994-1996, British Columbia rates of breast cancer were high. However, mortality from breast cancer in British Columbia was among the lowest in Canada. (Figure 3).

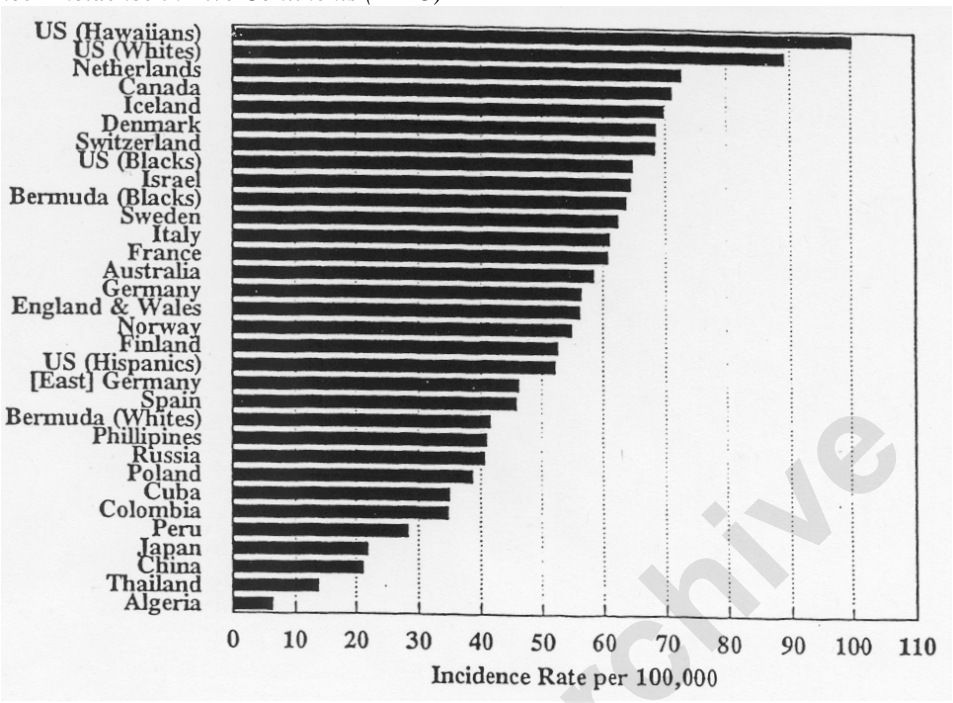
Figure 3. Incidence and Mortality rates of Breast Cancer in Canada (1984-1994/1996)
Source: Cancer Bureau, Laboratory Centre for Disease Control, Health Canada, based on data supplied by Statistics Canada (April 1999) http://www.phac-aspc.gc.ca/publicat/updates/breast-99_e.html



According to estimations, in the year 2004, over 215,990 American women were diagnosed with breast cancer, and 40,580 women died because of this disease [12]. Recent analysis, performed by the Surveillance, Epidemiology, and End Results (SEER) program at the National Cancer Institute (US) shows that the lifetime probability of developing breast cancer is one in six, and for invasive breast cancer, it is one in nine [13].

Globally, the breast cancer incidence is highest in North America and Northern Europe and lowest in Asia and Africa (Figure 4). Incidence rates in Japan and urban China have been rising in recent years. Variation in international differences is believed to be related to societal changes which occur as part of industrialization (e.g. changes in fat intake, body weight, age at menarche, and/or lactation).

Figure 4. Age-adjusted annual breast cancer incidence rate among women in selected countries in 1983-87. Source: Cancer Incidence in Five Continents (IARC)



In general, breast cancer mortality increased steadily from the 1940s until the early 1980s (by 1.2 present per year) when the rates declined in most countries including Canada [14,15]. These declining mortality rates are thought to be related to improved screening resulting in earlier detection and improved treatment (especially increasing mammography use, since the incidence of stage one carcinomas increased, while that of higher stages either decreased or remained stable). As of 1987, breast cancer incidence rates were fairly stable [16]. Recent data analysis from the SEER program, however, suggest that the incidence of oestrogen (ER) and/or progesterone (PgR) receptor-negative breast cancer is declining while that of ER/PgR-positive disease is increasing [17]. Some of this increase is believed to be attributable to increased use of hormone replacement therapy (HRT) [18]. SEER data also have identified similar rates of ductal cancer incidence but a two-fold higher proportion of lobular cancers over the period between 1987 and 1999, an interesting finding in view of case control studies that link HRT to lobular cancers [19,20].

Analysis of migration patterns in the United States suggests that genetic factors alone could not be sufficiently accountable for the global variation in incidence. Incidence rates of breast cancer were found to be generally larger among second-generation migrants, and rises further in third-

and fourth- generation migrants. This information suggests that environmental and lifestyle determinants are important factors of breast cancer risk [21,22].

Mortality rates from breast cancer have been stable since 1950, although mortality rates of various subgroups have changed. The mortality rate for white women under age 55 has decreased, while it has increased for women age 55 and older [23]. The reasons for the decrease in the former are suspected to be related to the increase in mammography use in younger women and the aggressive use of adjuvant therapies. Mortality rates have increased in African-American women of all ages. Mortality rates are highest in the very young (less than age 35) and the very old (greater than age 75).

Breast Cancer Risk Factors

Sociodemographic Factors

A number of sociodemographic factors are associated with breast cancer risk. Most of these are likely surrogates for lifestyle, hormonal, and/or reproductive factors [24]. In terms of gender, beast cancer occurs one hundred times more frequently in women than in men. Male breast cancer in 2004 in the US is responsible for 0.2 percent of all cancers, and less than 0.1 percent of all cancer deaths in men annually [12].

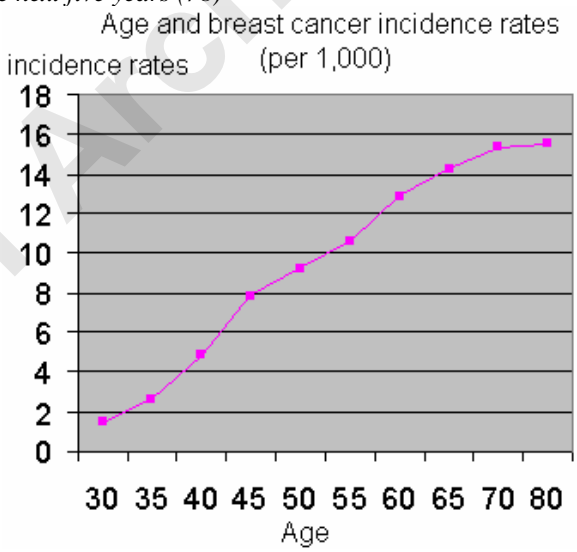
Age is major risk factor for breast cancer and (Figure 5) demonstrates the increased likelihood of a woman developing breast cancer in the next five years at various ages [25]. Incidence rates rise very sharply with age until about the age of 45 to 50 when the rise is less steep. This change in slope probably reflects the impact of hormonal change (menopause) that occurs about this time, although alternative hypotheses have been proposed [26]. At age 75 to 80, the curve flattens and decreases slightly thereafter [27]. Amazingly, age was the only identifiable risk factor in 76% of women who developed a breast cancer [28].

Females of higher socioeconomic status are considered to be at greater risk for breast cancer. There may be as much as a two-fold difference in incidence from the highest to the lowest classes. The influence of socioeconomic status (educational, occupational, and economic level) are thought to be mediated by differing reproductive patterns with respect to parity, age at first birth, and age at menarche [29]. In epidemiological studies higher socioeconomic status, as measured by income and education level, are consistently associated with elevated breast cancer

risk [4,30]. Although some of this association may be due to a clustering of reproductive risk factors in higher socioeconomic status women, the effect is still significant even after controlling for parity, age at first child and other common reproductive factors [31]. Diet has been well studied but epidemiological investigations have yet to identify foods that significantly increase or decrease breast cancer risk [32]. It is hypothesized that dietary factors may modulate hormone levels so a number of investigations have focused on foods high in phytoestrogens [33,34] (partial oestrogen agonists) or containing other endocrine active components [31]. Incidence and mortality rates vary throughout the North America, with the highest reported incidence in Hawaii (128 per 100,000 women) and lowest in Utah (98 per 100,000 women) [35]. Urban rates exceed those of rural areas. These differences are thought to be accounted for by differences in parity and age at first live birth, at menarche, and at menopause [26].

Figure 5. Probability of developing breast cancer in the next five years (78)

Age	Breast cancer (per 1,000)
30	1,5
35	2,6
40	4,8
45	7,8
50	9,2
55	10,6
60	12,9
65	14,3
70	15,4
80	15,5



In North America, breast cancer is the most common cancer among women of every major ethnic group, although there are interracial differences. California, as an example, has the highest rates among Caucasians (110.6 cases per 100,000 women). The rates in African-American women (96 per 100,000), Latina women (59.2 per 100,000), Asian-Americans (58.2 per 100,000), and others are lower [36]. Most of these ethnic difference are attributable to factors associated with lifestyle and socioeconomic status, which partially could explain differences in treatment and survival [37].

Inherited Risk Factors

Hereditary risk factors for breast cancer are multifactorial, and should not be simply understood as just a passage of genetic material. Hereditary factors are traditionally identified through thorough family histories. Only 10 percent of women diagnosed with breast cancer have a positive family history. The risk associated with having an affected first or second degree maternal or paternal relative is modulated by the age of both the case patient and the family member at diagnosis, and the number of first-degree relatives. In a meta-analysis using data from over 50,000 women with breast cancer and 100,000 controls, the risk of breast cancer for a woman with one affected first degree relative was increased 1.80 times. With the two affected first degree relatives, the risk is increased 2.93 times. The risk ratios (relative risk) were found to be highest in females with young affected relatives. Therefore, the risk was increased 2.9 times for a woman whose relative was diagnosed before age 30, but only 1.5 times increased if the affected relative was diagnosed after age 60 [38]. The risk of breast cancer before age 40 was increased 5.7-times if one relative had breast cancer before age 40. The question as to what extent the influence of a shared environment or a shared lifestyle contributes to the history of cancer is still open [39,40].

Inherited genes with a low penetrance may account for a familial-specific metabolism of DNA toxins, which in turn initiates or promote breast cancer. Identification of these genes may be difficult; however, their expression may be influenced significantly by differences in the environment. Mutations in BRCA1 and BRCA2 are strong with little respect for environmental differences. Studies in twins suggest that the majority of familial aggregation of breast cancer results from inherited susceptibility [41,42]. However, specific genetic mutations that predispose to breast cancer are rare. It is believed that only 5 to 10 percent of all breast cancers are associated with a specific gene mutation, such as BRCA1, BRCA2, p53, ATM, PTEN, MLH1, or MSH2.

The extent of dense tissue within the breast has recently found to be another risk factor. Breast density varies within the population, and appears to be largely inherited [43]. Besides increasing the difficulty of detection through mammography, the presence of dense breast tissue increases the risk of breast cancer by a factor of 1.8 to 6-times compared to women of similar age with less extensive dense tissue [44].

Breast Conditions

Benign breast conditions include a wide spectrum of pathologic entities. The important precursors of non-invasive or invasive breast cancer are grouped as proliferative disease with or without atypia. Non-proliferative lesions are not associated with an increased risk for breast cancer [24]. Poliferative lesions without atypia include fibroadenoma, moderate or florid hyperplasia, sclerosing adenosis, and intraductal papillomas. Women with these lesions typically have an increased risk of breast cancer of only 1.3 to 2 times that of the referent group [45,46] . Proliferative lesions with atypia (both lobular and ductal) possess one or more characteristics of carcinomas in situ and are associated with a higher relative risk of breast cancer development. The relative risk of invasive breast cancer (which is in majority of cases is ipsilateral) is associated with atypical ductal hyperplasia and ranges from four to six-fold [45,46]. These lesions are considered precursors of invasive breast cancer, although invasive disease does not develop in all cases [47]. Although historically regarded as an indicator of the risk of developing invasive breast cancer in both the ipsilateral and contralateral breast, results from a recent paper suggest that both atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS, a lesion that is qualitatively similar to ALH but more developed quantitatively) are not only indicators of increased risk, but indeed precursors of invasive cancers. The relative risk of invasive breast cancer with ALH ranges from three- to fivefold [45-48]. The risk for developing breast cancer in either breast in women with LCIS is 1 percent per year and persists indefinitely.

Malignant breast conditions that increase the risk of a new unrelated breast cancer include ductal carcinomas in situ and invasive carcinomas. With in situ lesions, the ten-year risk of developing an invasive breast cancer in the contralateral breast is 5 percent [21]; the risk of developing contralateral breast cancer in women with an invasive cancer is 1 and 0.5 percent per year for pre- and postmenopausal women, respectively.

Hormone Factors

Epidemiological and animal studies consistently show elevated risk of breast cancer with factors that increase exposure to estradiol, progesterone, and other hormones [33,49-51]. Risk factors such as alcohol consumption, weight gain after menopause, low pre-menopausal body mass index, and lack of physical exercise are believed to be associated with exposure to reproductive hormones [16,52-54]. Pharmaceutical hormones appear to have a similar effect and there is evidence

that women exposed to diethylstilbestrol during pregnancy had increased risks for breast cancer [12,13]. For oral contraceptives, recent use, not long term exposure, has been associated with an increased risk [16,17]. Similarly, recent use of hormone replacement therapy has been shown to increase the relative risk of breast cancer, whereas women who stopped over 5 years ago are not at significantly elevated risk [18].

Prolonged exposure to, and higher concentrations of, endogenous oestrogen will increase the risk of breast cancer. The production of oestrogen subtypes (estradiol, estriol, estrone) is modulated by ovarian function: menarche, pregnancy, and menopause. After menopause, the main source of oestrogen is dehydroepiandrosterone (DHEA), which is produced in the adrenal gland and metabolized in peripheral fat tissue to estradiol and estrone [55]. The roles of progestins, prolactin, and insulin-like growth factor are less clearly established.

Important factors that influence breast risk are age at menarche, age at first live birth, age at menopause, and possibly parity and breast-feeding [22,56,57]. Younger age at menarche is associated with a higher risk for developing breast cancer [58] . One study found that for every two year delay in the onset of menarche there was a 10 percent reduction in breast cancer risk [59]. Others have shown in a case control study of disease-concordant monozygotic twin pairs that the twin with earlier onset of menses was five times more likely to be diagnosed with breast cancer before the other [60]. In contrast, other hormonal factors (ie, later first pregnancy, lower parity, later menopause) did not predict an earlier diagnosis when both twins were affected. The explanation for this protection is that late onset of regular menstrual cycles is associated with later exposure and thereby less lifetime exposure to hormones.

There is an inverse association between the age at first pregnancy and risk of breast cancer [56]. However, women who give birth to their first child after the age of 30 have a higher risk than nulliparous women. Women giving birth for the first time at age 35 have a 1.6 times higher risk of breast cancer than women first giving birth at age 26 to 27 [58,61]. The explanation for the effect of early first live birth is that full cellular differentiation, which occurs in the gland during and after pregnancy, protects it from breast cancer development.

The association between the age of menopause and the risk of breast cancer is straight - the later a woman undergoes menopause the higher her risk for breast cancer [58]. Bilateral oophorectomy

before the age of 40 reduces lifetime risk by 50 percent [60]; however, this risk reduction is eliminated if replacement estrogens are given. The association between late menopausal age and increased breast cancer risk is thought to reflect longer exposure to the endogenous higher pre-menopausal levels of hormones [56]. Nulliparous women are at increased risk for breast cancer compared with parous women [58]. The risk ranges from 1.2 to 1.7 and appears to affect women after the age of 40 to 45 [56]. Whether multiparity confers protection against breast cancer has been a matter of controversy; the most recent studies suggest a decreased risk with increasing number of pregnancies [61]. Abortions have been hypothesized to increase breast cancer risk. One meta-analysis of case-control studies supports this theory [62], but the other does not [63]. Population based cohort studies (an epidemiological stronger design) do not support this association [64-66]. In March 2003, the National Cancer Institute accepted the findings of a workshop evaluating the link between early reproductive events and breast cancer, which concluded that induced abortion is not associated with an increase in breast cancer risk (available at www.cancer.gov/cancerinfo/ere).

Full term pregnancy is thought to be associated with an increased breast cancer risk. The protective effects of pregnancy are not seen until after ten years following delivery [67]. Other studies shows that placental factors like maternal floor infarction, smaller size and pre-eclampsia during pregnancy are associated with a reduced incidence of maternal breast cancer [68]. Breastfeeding was shown to be protective against breast cancer in multiple case-control and cohort studies, the magnitude of which is dependent on the duration of breastfeeding, and on the confounding factor of parity [58,61,69-71]. In the largest case-control study that included individual data from 47 epidemiologic studies including 50,302 women with invasive breast cancer and 96,973 controls, the relative risk of breast cancer was reduced by 4.3 percent for every 12 months of breast feeding, in addition to a decrease of 7 percent for each birth [71]. Furthermore, it was estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than one-half (from 6.3 to 2.7 per 100 women by age 70) if women had the average number of births (6.5 versus 2.5) and a lifetime duration of breastfeeding (24 versus 3 months per child) that had been prevalent in the past. Two-thirds of this estimated reduction was attributable to longer duration of breastfeeding. The mechanism postulated for the protective effect of breastfeeding is that it may delay the re-establishment of ovulatory cycles. Other

mechanisms may be the increase in prolactin secretion and the concomitant decrease in estrogen production [24].

Hormone levels were shown to promote breast cancers in animals, and various studies have manipulated hormones to demonstrate this point [72]. Few studies have prospectively examined the relationship between serum estrogen concentrations and breast cancer risk in humans; much of the available evidence is primarily based upon observational data. Obese postmenopausal women have higher oestrogen levels, due to the conversion of adrenal androgens to estrogens in fatty tissue, and are at increased risk of breast cancer [73]. Reducing oestrogen levels (by castration or use of antiestrogens such as tamoxifen) lowers breast cancer risk. Despite these observations, the correlation between breast cancer risk and hormone levels from studies examining blood or urine samples have not been consistent, in part due to the inter-individual and intra-individual variability of hormone concentrations and difficulties with the assays. Oestrogen levels fluctuate during menstrual cycles and pregnancy, making reproducible measurements difficult in the pre-menopausal years. Furthermore, most epidemiologic studies have tended to use a single blood sample. Thus, it is not surprising that the data on pre-menopausal women are limited and inconclusive. The data on oestrogen metabolites are similarly limited [24].

A 2002 review of several prospective epidemiologic studies found a positive relationship between serum estradiol concentration and breast cancer risk [74]. Similar results were obtained a study of 7705 postmenopausal women enrolled on the Multiple Outcomes of Raloxifene Evaluation (MORE) trial: women with the highest tertile of serum estradiol levels (>12 pmol/L) had a two-times higher risk of invasive breast cancer than women with lower levels [66]. Also, females in the highest estradiol tertile tended to have a greater reduction in the risk of breast cancer with raloxifene compared to women in the low estradiol subgroup (79 versus 64 percent). Results of the Nurses' Health Study suggest that the association is strongest for hormone receptor-positive breast cancers [75]. In this longitudinal study of 121,700 female registered nurses in the US, endogenous hormone levels were measured in 322 women who developed breast cancer and in 643 age-matched controls without breast cancer. When the highest and lowest quartiles of serum hormone concentration were compared, there was a significant direct association between breast cancer risk and levels of both estrogens and androgens. The strongest

association was found when the analysis was limited to ER and PgR-positive tumors, and in situ tumours.

Since bone tissue contains oestrogen receptors and is highly sensitive to circulating oestrogen levels, bone mineral density (BMD) was thought to be a surrogate marker for long-term exposure to endogenous oestrogen. In the report of elderly women with high BMD it was found that higher BMD is associated with the greater risk of breast cancer (relative risk 2.7 for women in the highest compared to the lowest quartile of BMD), compare to women with lower BMD [76].

Postmenopausal females with higher testosterone levels may be at a higher risk of breast cancer [74,75,77-79]. Studies of oprogesterone, prolactin, insulin, and insulin growth factor are limited. However, resent publications suggest a possible increased risk of breast cancer with higher serum levels of insulin-like growth factor I (IGF 1) and its main binding protein IGFBP-3 in pre-menopausal but not postmenopausal women [80,81]. Some, but not all, studies suggest a slightly increased risk of breast cancer in postmenopausal but not pre-menopausal women with type 2 diabetes.

There is a rising concern regarding increased risk of breast cancer with usage of oral contraceptives (OC), infertility treatment and hormone replacement therapy (HRT). Several epidemiologic studies have not demonstrated any association between OC use and the risk of breast cancer. However, a large meta-analysis (conducted in 1996) calculated a small but significant increase in relative risk of breast cancer (RR =1.24) in current oral contraceptive users [82]. Concerns have been raised about this meta-analysis because a low percentage of women had 'ever' used oral contraceptives (40 percent), and it lacked the follow-up necessary to determine whether there were long-term effects of oral contraceptive use. There are now reassuring data from two studies that oral contraceptives do not increase breast cancer risk later in life [83,84].

Causal relationship between the usage of HRT and increased risk of breast cancer has been supported in the current literature, mostly hormone receptor-positive breast cancer [85]. The risk is small but was consistently demonstrated. Oppositely, a trend towards lower breast cancer risk was observed in women taking unopposed oestrogen (HR 0.77 for unopposed oestrogen vs. placebo, 95% CI 0.59-1.01) [86]. Long-term use of HRT is associated with the highest risk. In

contrast, short-term HRT appears not to increase the risk of breast cancer significantly, although it may make detection through mammography more difficult. Concurrent progestin use appears to further increase risk above that with estrogen alone [87].

Prevention of Breast Cancer

All major North American groups making recommendations about breast cancer screening recommend routine screening with mammography with or without clinical breast examination for women aged 50. In the 1996-1997 National Population Health Survey, 79% Canadian women 50-69 years of age report having had a mammogram. The proportion of women in this group reporting ever having had a mammogram is between 75% and 82% in all provinces except Nova Scotia (64%) and Newfoundland (54%). Eighty-five percent of those who had a mammogram in at least 2 years report having had one of the following reasons: routine check-up, family history, age, or hormone replacement therapy. Low education and income are associated with fewer mammograms of any type [88].

The Screening Mammography Program is the major preventive health program for British Columbia women. Currently, between six and eight women out of 10 do not use this program that costs the system more than $6 million per year. The Minister's Advisory Council on Women's Health expressed the need to make this program work more effectively or reconsider its utility in light of other competing priorities. [89]. At present, the best preventative strategy for breast cancer is early detection. Women who detect the breast cancer in situ have a 95 percent survival rate; if it is not detected in the breast and has metastasized to the rest of the body, survival rates are much lower [89]. Although the Canadian Cancer Society emphasizes a three-step process involving a monthly breast self-exam, an annual clinical breast exam and mammography, the Ministry of Health or the Screening Mammography Program do not monitor the practice of all three aspects of care. Data from the North Shore health unit's 1990 health promotion survey indicated that only 30 per cent of women practice monthly breast self-exam [90]. By health region in British Columbia, the percentage of women aged 50 and older who received mammogram in 1992-93 ranged from 20 percent (upper Fraser Valley) to 39 present (South Central). Another way of saying this is, at the present time, between six and eight women out of 10 in British Columbia do not participate in this publicly-funded preventive health program [90].

Occupational and Environmental Factors in Breast Cancer

Recent animal studies provided important information in understanding mechanisms of the development of breast cancer and in the identification of agents that may increase breast cancer risk. A comprehensive review of chemical carcinogenesis in general is beyond the scope of this paper. Based on human epidemiological studies, ionizing radiation is one of the few occupational or environmental exposures that are known to cause breast cancer [19,20], although it should be noted all cancer causing agents, physical or chemical, will also have the potential to initiate or promote cancer.

Cells within the breast are not fully differentiated until they are induced by hormonal stimuli at the woman's first pregnancy and lactation. Thus, breast cells are more susceptible to the effects of carcinogens while the breast is not fully developed. Additionally, the breast cells are vulnerable to genotoxic agents during pregnancy as there is rapid proliferation of cells [27,91]. This explanation of the susceptibility of mammary cells to carcinogens provides a framework for understanding the increased risk of breast cancer in humans in relation to reproductive events as well as after exposure to mammary carcinogens. It has been hypothesized that, because the breast is very susceptible to carcinogen exposures up until the first full-term pregnancy, there may be an interaction of age (a known risk factor) and the risk associated with exposures to chemicals [29].

Despite the complex mechanisms and interactions between chemical exposures and hormones, animal studies have clearly identified numerous mammary carcinogens through standard cancer bioassays. The US National Toxicology Program (NTP) has tested over 500 chemicals and identified 42 as causing mammary tumours [35]. The human evidence for identifying chemicals causing breast cancer is more scant and of the 42 chemicals cited above, only four are classified as human carcinogens: benzene, 1,3-butadiene, ethylene oxide, and C I acid red 114. Also, it should be noted that epidemiology studies of these compounds have shown exposed employees at higher risk of cancer, but not specifically breast cancer. Mammary carcinogens that may be associated with exposures in chemical and medical laboratories are presented in Table 1 below.

Both animal and human studies show that the relationships between hormonal factors and mammary carcinogens are complex. Treatment of animals with ovarian, placental, pituitary, and thyroid hormones modulates the tumorgenic responses [26]. The situation is further complicated

with exposures to chemicals that are members of a class of hormonally active chemicals, sometimes referred to as endocrine active, endocrine disruptors, or estrogenic compounds. The hypothesis is that exposure increases oestrogen-like responses of cell proliferation that increase cancer risk. There is also a concern that these endocrine active compounds can act in an additive manner to produce effects [29,36].

Table 1:Chemicals tested by NTP that produce mammary tumors in experimental animals[4]

Chemical	Use
Acronycine	Pharmaceuticals
Benzene	Gasoline, solvent
2,2-bis(bromomethyl)- 1,3-propanediol	Flame retardant
1,3-Butadiene	Auto exhaust, rubber manufacture, gasoline
C,1 acid red 114	Dye for silk, jute, wool, leather
C,1 basic red 9 monohydrochloride	Dye for textiles, leather, paper, biological stain
2-Chloroacetophenone	Flame retardant
Chloroprene	Used in neoprene manufacture
Clonitralid	Molluskicide
Cytembene	Pharmaceuticals
2,4-Diaminotoluene	Intermediate in dye synthesis
1,2-Dibromo-3-chloropropane	Soil fumigant, pesticide
1,2-Dibromoethane	Soil fumigant, lead scavenger in gasoline
1,2-Dibromo-1-propanol	Flame retardant
1,1-Dichloroethane	Solvent
1,2-Dichloroethane	Solvent, chemical intermediate in insecticide formulations, gasoline
1,2-Dichloropropane (propylene dichloride)	Chemical intermediate, solvent in dry cleaning fluids, fumigant
Dichlorvos	Pesticide
1,2-Dimethoxybenzidine dihydrochloride	Dye intermediate
3,3-Dimethylbenzidine dihydrochloride	Dye intermediate
2,4-Dinitrotoluene	Dye intermediate, explosives, propellants
Ethylene oxide	Sterilizing gas for medical equipment
Furosemide	Pharmaceuticals
Glycidol	Stabilizer in vinyl polymers, intermediate in pesticides and fragrances
Hydrazobenzene	Dye intermediate, tobacco pesticides, motor oil
Isophosphamide	Pharmaceuticals
Indium phosphide	Microelectronics, semiconductors, injection lasers, diodes
Isoprene	By-product of ethylene production
Methylene chloride	Solvent, furniture stripper, adhesives
Methyleugenol	Food additive, flavoring, also naturally occurring
Nithiazide	Antiprotozoal compound
5-Nitroacenaphthene	Research chemical
Nitrofurazone	Antibiotic
Nitromethane	Rocket and engine fuel, solvent, mining explosive
Ochratoxin A	Mycotoxin
Phenesterin	Pharmaceuticals
Procarbazine hydrochloride	Pharmaceuticals

[4] From 35. Bennett LM, Davis BJ. Identification of mammary carcinogens in rodent bioassays. *Environ Mol Mutagen* 2002;**39**(2-3)**:**150-7.

Reserpine	Pharmaceuticals
Sulfallate	Herbicide
2,4- and 2,6-Toluene diisocyanate	Used in manufacture of flexible polyurethane foams
o-Toluidine hydrochloride	Dye intermediate
1,2,3-Trichloropropane	Chemical intermediate, former solvent and paint remover

Chemicals, including some pesticides, also can act as co-carcinogens or tumuor promoters [37]. A good example of a breast cancer promoter in experimental animals is dichlorodiphenyltrichloroethane (DDT). Experimental animals fed a known mammary carcinogen, and then given DDT, developed breast tumuors earlier than when the carcinogen was given alone; however, when DDT was given alone, it did not induce breast tumuors in these animals [39]. The human evidence of DDT's effects as a promoter is more equivocal, although a recent study reported significantly elevated mean levels of serum DDT and hexachlorobenzene (HCB) in breast cancer patients as compared to controls [40]. Other organochlorine compounds have been implicated as being associated with an increased risk of breast cancer. The hypothesis is that this group of compounds possess estrogenic activity. However, both the hypothesis and the magnitude of any possible effect on human risk of breast cancer is controversial. Recent reviews suggest that the estrogenic contribution of organochlorine compounds is small in view of the presence of natural hormone and anti-hormone mimics in our diet [21,92]. Other endocrine active compounds, such as alkyl phenols and phthalates are still under investigation [41].

Studies of breast cancer risk in working populations have not provided strong evidence of causal links between specific exposures and increased risk. However, there is evidence for positive associations of several occupations with increase breast cancer risk [42,93,94]. The study by Band et al. (2000) was conducted in British Columbia and found significantly higher breast cancer risks [42] among *pre-menopausal* women in electronic data-processing operators; barbers and hairdressers; in sales and material processing occupations; and in the food, clothing, chemical and transportation industries. Among *post-menopausal* women, an elevated risk was found in school teaching; in medicine, health, and nursing occupations; in laundry and dry-cleaning occupations; and in the aircraft and automotive, including gasoline service station, industries. Several significant associations were also seen in the combined group of pre- and post-menopausal women, particularly in crop farmers and in fruit and vegetable farming, publishing and printing, and motor vehicle repair industries. The authors suggested that there was excess

breast cancer risk in a number of occupations and industries, notably those that entail exposure to solvents and pesticides [42].

Shift work causes employees to have exposure to light at night and may increase the risk of cancer by suppressing the normal nocturnal production of melatonin by the pineal gland. Melatonin is not only a hormone that has anti-proliferative effects which protect against the development of cancer [95], but it also modulates oestrogen release from the ovaries. When nocturnal melatonin production is suppressed, the direct anti-proliferative effects are reduced and oestrogen release may be increased. There are a few studies that support an association between exposure to light at night and the risk of breast [95]. However, the strength of the association has been variable (Figure 6).

A nationwide population-based case control study included 7035 Danish women with breast cancer and individually matched controls [96]. Among women aged 30 to 54, the OR for breast cancer among those who worked at night for at least six months was 1.5, with a trend toward increased OR for longer durations of night time employment. Similar findings were noted in another case control study: OR 1.6 for night time shift work, with a trend toward higher risk with more years and more weekly hours of nocturnal shift work [97]

A more modest association between night time shift work and breast cancer risk was noted in a prospective cohort series from the Nurses' Health Study [95]. The relative risk of breast cancer was significantly increased only among women who worked rotating night shifts (at least three nights per month) for 30 years or longer (RR = 1.36).

Figure 6. Studies, investigated association between night time shift work and breast cancer risk

Author	Year	Subjects	Findings	OR / CI
Tynes T, et al.	1996	2,619 Postmenopausal tele /radio operators exposed to nightshifts	F > 50 y.o. are at ↑ risk of BC	OR=4.3; 95%CI (0.7-26.0)
Pukkala E, et al	1995	Flight attendants (50 cases, 259 controls)	Lifestyle of F cabin attendants ↑ risk of BC	SIR=1.87; 95%CI (1.15-2.23)
Nabsen J.	2001	Matched case-control (7035 Danish F)	F who work @ night for at least 6 mo are at ↑ risk of BC	OR 1.5; 95%CI (1.2-1.7)
Davis S	2002	813 F cases (20-74) with BC; 793 controls	F exposed to LAT ↑ risk of BC	OR = 1.14 for each night per week; 95% CI (1.01 - 1.28)
Kliukiene J et al.	2001	15,412 Norwegian visually impaired women.	Blind F are at ↓ risk of BC	SIR = 0.51 (95% CI = 0.11-1.49).

It is postulated that exposure to light at night suppresses the normal nocturnal production of melatonin by the pineal gland, which in turn, could increase the release of oestrogen by the ovaries. In one of the above studies, the risk of developing breast cancer was significantly higher in women who did not typically sleep between 1 AM and 2 AM, the night time period when melatonin levels are at their highest (OR 1.14) (62).

Breast Cancer Risk among Laboratory Workers

Clinical laboratory workers have the potential for exposure to a variety of potentially harmful chemical, biological, as well as physical agents including solvents, radioisotopes, chemical carcinogens, viruses, bacteria, human and animal tissue samples and lately also recombinant organisms. [43,44,46]. Despite the fact that chemical and clinical laboratories employ many women (over 1 million in the US) few studies have examined the possible adverse effects of exposures on this occupational group.

Wennborg et al. (2005) investigated congenital malformations related to maternal exposure to specific agents in laboratory employees. The study involved 1951 females and the authors found that the prevalence of "major malformations" were 2.3% (n = 41; exposed) and 1.9% (n = 23; unexposed). For the major malformations, solvent exposure before the third trimester gave an odds ratio (OR) of 1.8 (confidence interval (CI) = 1.0-2.9); "laboratory work in general" of 1.2 (CI = 0.7-2.0). The OR for benzene use around conception/organogenesis was 5.3 (CI = 1.4-

21.1) for non-conditioned medium (NCM). No significant risk for laboratory work in general was seen, but there was an increased ratio for NCM relative to solvents, especially benzene [98].

Wennborg (2000) compared mortality and cancer incidence in 5,035 full time laboratory employees with a cohort of 2,923 employees of non laboratory departments at Karolinska Institute and at the Universities of Lund, Gothenburg and Linköping. Findings shown that the total mortality as well as the incidence of all cancers together was lower in both the laboratory and the non-laboratory groups than in the general population, but slightly (non significantly) increased risks were seen for male brain tumours (SIR=3.11 (95% confidence interval 0.85-7.96) after 10 years of work), and female breast cancer among laboratory personnel (standardized incidence ratios (SIR)=1.62 (CI 0.78-2.98). Work with solvents showed an elevated SIR of malignant melanoma in female laboratory personnel. Concerning reproductive health, no major risks were noted for most outcomes. However, mother's work in laboratory showed an increase of large for gestational age (LGA) infants and an association was seen between reduced fecundity and use of solvents, cell techniques or viruses [99].

Burnett et al. (1999) conducted a study to determine if laboratory workers in the US experienced higher cancer mortality rates than those in other occupations. They found that clinical laboratory workers had higher proportionate cancer mortality ratios overall (for all cancers) as well as for breast cancer. The proportionate mortality ratios for leukaemia were also significantly elevated for clinical laboratory workers [45]. The authors suggest that the elevated risks for lymphatic and hematopoietic neoplasms may have been associated with occupational exposures.

Brown et al (1996) conducted a cohort study among 12,703 individuals employed by biological research institutes in the UK. Authors found that mortality due to all causes was significantly reduced in men (standardised) mortality ratio (SMR) 55 and women (SMR 52). Mortality was also significantly reduced for circulatory and respiratory diseases, and overall there was low mortality from malignant neoplasms. SMRs exceeded 100, but were not statistically significant, for infective and parasitic diseases. There were no statistically significant raised SMRs for any cancer site. Workers were categorised as ever worked in a laboratory (laboratory workers) and never worked in a laboratory (non-laboratory workers). The all-cause SMR was significantly reduced in both groups, as was mortality from circulatory and respiratory diseases. The SMR for malignant neoplasms was also significantly reduced in laboratory workers [100].

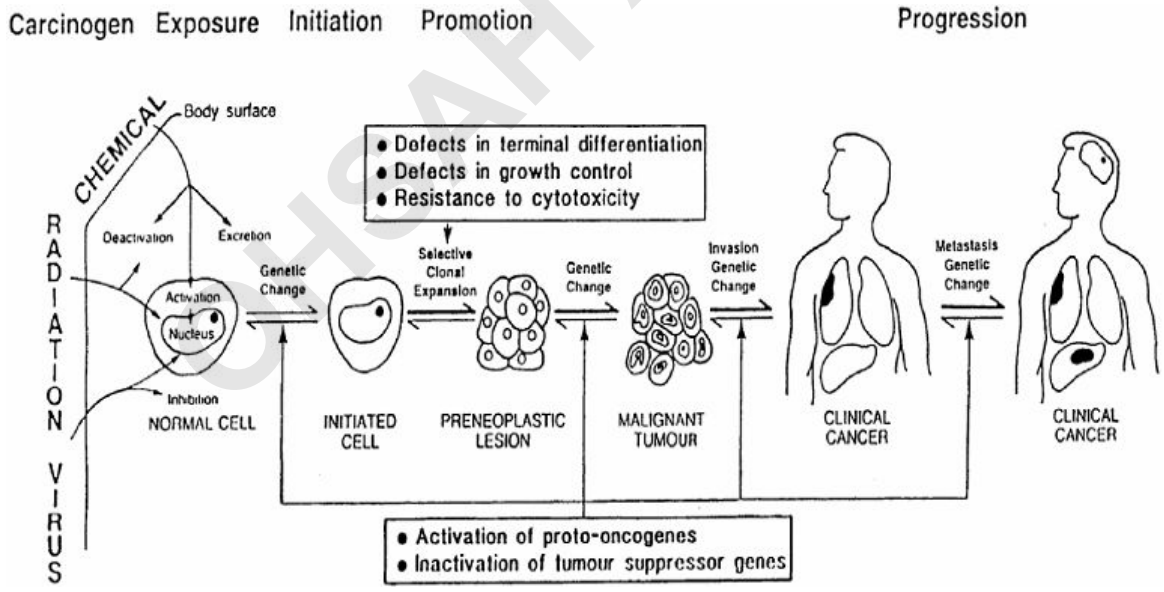
A recent large-scale cohort study conducted by van Barneveld et al, (2004) among 7,307 laboratory workers in the Netherlands, found that laboratory workers have a favourable cancer mortality pattern as compared to the general population. Authors commented that all-cause mortality among laboratory workers was significantly lower than that in the general population. Total cancer mortality and lung cancer mortality were also significantly decreased (SMR=0.8; 95% confidence interval CI=0.7–0.9 and SMR=0.7; 95% CI=0.6–0.9), respectively. However, when compared to the internal reference population, laboratory workers had a slightly, non significantly, increased cancer mortality (relative risk (RR)=1.3 95% CI=0.9–1.9). Among men, a 2.5-fold (95% CI=1.0–6.3) increase of lung cancer mortality was observed which could not be explained by differences in smoking habits. Lung cancer mortality increased with longer follow-up. Results with regard to a priori defined fields of research showed significantly increased cancer mortality (in particular from lung cancer) for men working in genetics (RR=3.8), virology (RR=4.1) and plant physiology (RR=2.1). Authors concluded that the excess lung cancer mortality among male laboratory workers was concentrated in certain fields of research, which warrants further research to identify specific exposures related to the increased risk [101] .

Based on the assumption that laboratory work, especially in the area of biomedical research, is associated with exposure to a mixture of carcinogens, a group of Israel scientists conducted a two fold research aiming to analyze the cancer incidence among laboratory workers employed in biomedical research laboratories versus the employees at the routine laboratories. The first publication presented the results of the analysis of 4,300 laboratory workers whose cancer incidence was followed from 1960 to 1997. The authors found that work in research and biomedical laboratories might involve an increased risk of certain types of cancer. In fact, significantly elevated SIR was found in breast, ovary, and thyroid cancer among women; and prostate cancer, leukaemia, and melanoma among men [102]. The second publication from the same author aimed to examine whether the excess cancer morbidity that was found can be explained by exposure to a particular group of substances, taking into consideration potential confounders. This study (nested case control study) included 163 cases and two matched control groups: laboratory workers (311) and general population (448) workers. The authors employed multiple conditional regression analysis which showed that working in research laboratories involved an increased risk of cancer generally among women [risk ratio 2.2 (1.2-4.3)], and of breast cancer particularly [risk ratio 2.3 (1.1-4.7). Seventy-six percent (76%) of breast, 87% of

thyroid, 60% of ovary and prostate, 94% of melanoma, and 50% of leukaemia cases were ever exposed to at least one known human carcinogen. Authors believe that the results of this study exclude the possibility that the excess cancer morbidity was related to personal risk factors but they may be explained by exposure factors [103].

With the exception of a few studies that have identified very high occupational exposures to carcinogenic compounds as causal factors in breast cancer, most investigations have not been able to clearly determine occupational risk factors [93]. The reasons for the failure to identify specific chemicals or physical agents include not only the complex nature of the initiation, promotion, and development of breast cancer (Figure 7), but also the presence of many potential confounding risk factors. Additionally, there appear to be numerous, but so far unidentified, risk factors that the issue of confounding becomes even more salient. Little is known about the interaction of known risk factors on the magnitude of increase in breast cancer risk and even less is known about the possible synergistic, additive, or antagonistic effects of multiple chemical exposures.

Figure 7. Stages of carcinogenesis



The strength of already known breast cancer risk factors makes the identification of occupational risk factors very difficult. When examining the role of these major risk factors, it has been estimated that 41 percent of breast cancer risk is attributable to later childbearing, nulliparity, higher income, and family history of breast cancer [47]. Studies that have focused on genetic

variation have estimated that less that 10 percent of cases are due to gene mutations in the breast cancer genes *BRCA1* and *BRCA2* [48]. Diet, alcohol consumption, physical activity, body mass index, other reproductive factors, high chest radiation exposure, and exposure to pharmaceutical hormones all account for some risk in the development of breast cancer. In occupational studies, if the likelihood of exposure to these known breast cancer risk factors is increased in an occupational group, an association between the occupation and increased breast cancer risk will be observed. Conversely, the presence of powerful risk factors known to cause breast cancer may mask the effect of an occupational exposure that is truly increasing breast cancer risk, unless methods are used to "control for" time factors.

Traditional epidemiological methods are typically not able to identify occupational risk factors for breast cancer at the levels of exposure seen in modern industry in Canada or the US. Newer methods that include the use of biological markers of exposure and incorporating gene-environment interactions have shown promise. These methods are better able to uncover subtle differences in risk and also provide an understanding of the underlying mechanisms. An example of these cutting edge techniques is the measurement of the aromatic amine, *o*-toluidine, a rat mammary carcinogen, in human milk samples from mothers. The presence of this chemical indicates that the ductal epithelial cells of the breast are exposed to this carcinogen [21]. The use of biomarkers and gene-environment interactions have elucidated the complex associations of smoking, polymorphisms of drug metabolizing enzymes, and reproductive factors in breast cancer risk [21]. These techniques have not been rigorously applied in studies involving occupational exposures and breast cancer but their use has been advocated [21,55].

Incinerator Emissions and Cancer

Incineration is widely used in the United States and Canada to reduce the volume of waste. Whether waste incineration poses a health risk to incinerator employees or to people living and working nearby has been the subject of much debate. When operated properly by well-trained employees, modern waste incinerators pose little risk to public health. But older designs, human error, and equipment failure can result in higher-than-normal, short-term emissions that need to be studied further. A few studies have tried to establish a link between an incinerator and illness in the surrounding area, but most studies have been unable to detect any adverse health effects. The studies that did identify effects on health had shortcomings and failed to provide convincing

evidence. However, it should be noted that ailments may occur infrequently or take years to appear, pollution from other sources may also be present; these factors make it difficult to determine if waste incineration can indeed be responsible for local health problems [104].

Medical incineration systems are one of the growing public health concerns. In addition to infectious waste, hospitals burn disposable plastic medical and food items, office waste, packaging, and construction debris. Burning this waste could discharge poisonous substances including mercury, lead, acid gases, dioxins and other chlorinated compounds [105]. Many of these chemicals are known to be persistent, bio-accumulative, carcinogenic or endocrine disruptors. Most heavy metals have been reported to be associated with kidney disease, respiratory diseases, cardiovascular damage, blood effects, and neurotoxicity [106]. Some are classified as proven or suspected carcinogens (Figure 8). Some are associated with particular health effects [107]. Polyaromatic hydrocarbons (PAHs), released during the incomplete combustion or pyrolisis of organic matter, may have estrogenic properties [108] and are reported in association with ischemic heart disease[109] and cancer, in particular lung cancer [110] and bladder cancer [111].Polycyclic aromatics (PCA) have been reported to be mutagenic and mutagenicity was found to be inversely proportional to the degree of completeness of refuse combustion (188). Poorly controlled combustion processes can entail the production of dioxins, another class of compounds that include two families of chemicals, polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). These groups consist respectively of 75 and 135 cogeners that determine toxic effects on human health with different grades of severity [107]. Because of these concerns, hospital systems of disposing biomedical waste are under close observation and recommended to be updated periodically [112,113].

Figure 8. Carcinogenic effects of chemicals according to the IARC evaluation

Carcinogenic effects of chemicals according to the IARC evaluation

Ref.	Chemical	Chemical group	Degree of evidence in humans	Evaluation (IARC)	Carcinogenic effects
[51]	Arsenic	Metals	Sufficient / carcinogenic	1	Skin, lung, liver, bladder, kidney, colon
[52]	Beryllium	Metals	Sufficient /carcinogenic	1	Lung
[52]	Cadmium	Heavy metals	Sufficient /carcinogenic	1	Lung, prostate
[53]	Chromium (VI)	Metals	Sufficient /carcinogenic	1	Lung
[53]	Nickel	Heavy metals	Sufficient / carcinogenic	1	Lung
[52]	Mercury	Heavy metals	Inadequate	2B	Lung, pancreatic, colon, prostate, brain, kidney
[51]	Lead	Heavy metals	Inadequate	2B	Lung, bladder, kidney, digestive system
[51]	Benzene	Polycyclic aromatics	Sufficient / carcinogenic	1	Leukemia
[51]	Carbon tetrachloride	Chlorinated hydrocarbons	Inadequate	2B	Liver, lung, leukemia
[54]	Chloroform	Polycyclic aromatics	Inadequate	2B	Bladder, kidney, brain, lymphoma
[55]	Chlorophenols 55	Chlorinated aromatics	Inadequate	2B	Soft-tissue sarcoma, Hodgkin's and non Hodgkin's lymphoma
[56]	Trichloroethylene	Chlorinated solvent	Limited	2A	Liver, non Hodgkin's lymphoma
[57]	Dibenzo-para-dioxin	Dioxins	No adequate data	3	All cancer
[57]	Polychlorinated Dibenzo-para dioxins	Dioxins	No adequate data	3	All cancer
[57]	Polychlorinated dibenzofurans	Dioxins	Inadequate	3	All cancer

Franchini et al. (2004) published a comprehensive review of forty six epidemiological studies (published from 1987 to 2003) on health effect effects in populations living in the neighbourhood of waste incinerators [107].

The analysis done by Franchini et al. revealed significant exposure-disease associations. No clear association between breast cancer and exposure to incinerators or exposure to multiple sources including incinerators were reported. However, some studies have shown significant association with lung cancer. Two studies reported significant association between non-Hodgkin's lymphoma and environmental exposure to incinerators located in the UK and France and a significant increase in risk of soft tissue sarcomas was found in France and in Italy in association with residence close to waste incinerators. A UK study pointed out a small increased risk of liver cancer associated with living within 1 km of an incinerator even after adjustment for other known risk factors. A small area analysis of mortality among Italian residents near multiple sources of combustion products did not indicate any clear association between liver cancer mortality rates and distance from sources of exposure but highlighted an increase - though not significant - of cancer of the larynx in males as distance from the plants decreased and a significant excess of mortality for kidney cancer in females between 3 and 8 km from the exposure sources. (Cited by: Franchini M. et al) [107].

Cancer Cluster Investigations

Incidence rates of breast cancer, and all cancers, vary over time and geography and a cancer cluster is generally defined as the occurrence of a greater than expected number of cases of a particular cancer within a group of people, a geographic area, or a period of time. Studying and describing these spatial and temporal trends have provided clues for identifying previously undiscovered causes of cancer. In fact, the first causal relationship between an occupational exposure and cancer was uncovered as the result of a cluster investigation of scrotal skin cancer among young chimney sweeps in London [114]. Epidemiologists, the scientists most often leading the investigation of clusters, generally encounter clusters because of reports or through discovery from organized analyses of large databases [115]. Although the methods of analysis differ slightly depending on how the cluster is first identified, in both cases the results are difficult to interpret and drawing definitive conclusions is often not possible.

As was discussed in the section on breast cancer risk factors, some variation in breast cancer risk can be explained by the population distribution of known risk factors such as parity, age at first child and other reproductive factors [116]. In fact, grouping of reproductive risk factors and socioeconomic status play a major role in the findings of positive associations between white collar occupations and increased risk of breast cancer [29]. However, regional patterns of increased and decreased breast cancer risk may reflect a complex aggregation of diverse factors which may include diet, demographics, lifestyle factors, and occupational and environmental exposures. Gaining an understanding of these individual factors and their relationships is necessary to have a complete understanding of breast cancer risk in individuals and specific groups of women.

For breast cancer, clusters of relatively high incidence rates have been reported in areas of southern Alberta and British Columbia [117]. This type of variation by region is common and it is most often unclear whether or not the determinants of these differences are related to environmental, lifestyle, or other exposures. Even in populations that are well studied, such as in the Long Island, New York Breast Cancer Study Project [118,119], limitations in study design make the finding of significant environmental risk factors unlikely. In most investigations, biological data relating to occupational or environmental exposures is sparse or inadequate and other risk factors are not well controlled. Thus, even very extensive investigations of breast cancer clusters have high probabilities of failing to identify occupational or environmental risk factors [120].

Breast cancer cluster investigations are often limited because of the effect of the very strong risk factors related to endogenous hormones that increase breast cancer risk. The question still remains: do exposures to hormone-mimicking chemicals or other chemical and physical agents also exert an effect? A multidisciplinary workshop, titled "Hormones, Hormone Metabolism, Environment, and Breast Cancer," convened by the National Action Plan on Breast Cancer, the US National Cancer Institute, Tulane University, and the U.S. Public Health Service's Office of Women's Health, in September 1995 discussed the complexity of factors, unresolved controversial issues, and the need for improved methodology to measure hormones and their metabolites [121]. As is the case with occupational studies of breast cancer, molecular as well as bioinformatic techniques were discussed as useful tools in gaining an understanding of the complex relationships between genes, individual factors, and the environment.

Investigating Cancer Clusters: Methods and limitations

The first of the modern cancer cluster reports began in the 1960s and the increasing number of reports spurred the development of investigation protocols. At a US National Cancer Institute conference on clusters, Dr. Langmuir advocated a simple approach: "The constructive approach to this situation, in my opinion, is not to develop highly refined statistical techniques to determine whether or not a certain cluster may have resulted by chance alone. But, rather to investigate each cluster as it is reported and see if additional associations of possible interest can be found. If none turn up, this is obviously a cold trail, and any good hunting dog will abandon it, and look for a better one. If the scent strengthens, then hot pursuit is in order" [122].

Langmuir's advice for a simple approach did not deter the development of statistical models to resolve the issue of whether cancer cases were occurring independently or if they appeared to be related. A number of theoretical statistical methods have been developed and modified to detect clusters and to assess the statistical associations of interest. A detailed review of the theories underlying these sophisticated statistical approaches is beyond the scope of this discussion and interested readers should consult articles describing specific statistical techniques as well as comprehensive reviews of the subject [2,108,122-127]. Most of the models developed are useful when information is available on the observed cases in many discrete geographic locations and time intervals; the models then provide the likelihood of any one discrete location/time interval having a number of cases that is excessive. Thus, these techniques have most utility when there

is routine monitoring of cases across large geographic areas (i.e., province-wide or Canada-wide surveillance programs).

The detection and analysis of cancer clusters most often is the responsibility of public health agencies such as local health departments, state or provincial health authorities, cancer registries, or national health agencies (Health Canada or the US Centers for Disease Control (CDC)). The Canadian Cancer Incidence Atlas is a recently developed national atlas that assesses the significance and spatial correlation of the age-standardized rates for 290 census divisions across the country [128]. The Atlas provides information about cancer incidence rates and is able to determine if cancer rates are significantly elevated in certain areas. As discussed previously, the Lower Mainland of BC is one area in which breast cancer incidence rates are significantly elevated as compared to the national average [117].

When a cancer cluster is first reported, usually by concerned employees or citizens, the cluster is termed a *perceived cancer cluster*. If an investigation determines that the observed number of cases significantly exceeds the expected number it is termed an *observed cancer cluster*. If, after further investigation, a risk factor can be identified the cluster is called an *etiologic cancer cluster* [129]. In investigating cancer clusters the goal is to determine if the cluster is real (observed cancer cluster); and, if it is real, to determine if it is or is not an etiologic cancer cluster. If the investigation uncovers an etiologic cancer cluster, efforts should be made to reduce/modify the causal factors (exposures) that are responsible for the increased risk.

Public concern pertaining to environmental exposures and cancer resulted in the reporting of many perceived cancer clusters over the past 20 years [130,131]. Public health authorities responded to these concerns by conducting investigations that varied in scope and cost. Considerable resources were allocated to cluster investigations and most did not identify etiologic cancer clusters. The US CDC, from 1961 to 1982 investigated 108 reported cancer clusters in 29 states and 5 foreign countries; no clear cause of cancer was determined for any of the reported clusters [4]. The Minnesota Department of Health (MDOH) investigated more than one thousand cancer clusters between 1984 and 1995 without identifying a particular cause in any [132]. As a result of these many investigations, the MDOH developed a widely adopted systematic approach for cluster investigations [133,134].

Cancer clusters also occur in the workplace and a number of the classic exposure-disease relationships arose from investigations of clusters. The determinations that polycyclic aromatic hydrocarbons, asbestos, and vinyl chloride monomer are human carcinogens were made though analyses of cancer clusters in workers where these products were manufactured or used [114,135-137]. These etiologic clusters occurred before modern industrial hygiene controls were implemented and resulted from very high exposures to potent carcinogens. These early occupational cancer cluster investigations were effective in identifying and controlling large cancer risks that workers faced before the 1970s. Consequently, the role of occupational carcinogens in current clusters is more subtle than in the past and more difficult to detect.

In the US, the National Institute for Occupational Safety and Health (NIOSH), through its Health Hazards Evaluation Branch, is often called upon to investigate reported cancer clusters. In a review of 61 cancer clusters investigations that NIOSH completed between 1978 and 1984, a numerical excess of cases compared with expected numbers was found in 16 of the reported clusters [2]. In most of the reported clusters, no identified environmental exposure could be identified. In five of the 16 clusters there were exposures to potential carcinogens and the exposure-disease relationship was plausible (sufficient induction time and timing of exposure). Almost all of the investigations were limited by small numbers of cases, absence of complete personnel records, and other methodological and statistical issues that prevented the identification of specific causal occupational risk factors [2].

In Canada there have been few published cancer cluster investigations that have identified a specific cause that was occupationally related. The investigation of a cancer cluster in a steel mill in Ontario attempted to determine if occupational exposures to polycyclic aromatic hydrocarbons and silica were responsible for an increased risk of lung cancer. Even with extensive air monitoring data, no significant findings pertaining to environmental exposures were observed [138]. A more recent cluster investigation of an excess number of cancers within a police detachment in British Columbia involved the follow-up of 174 police personnel who where associated with the detachment since 1963 [139]. Sixteen cases of cancer were identified; however there was no evidence for an underlying event or exposure that could be attributed to the observed cancer cases. The authors discussed the possible role of police radar on the rate of cancer in the detachment.

Health agencies in the US, Canada, and Europe have established protocols for investigating reported cancer clusters. These protocols may differ in some of the specific steps but they do follow a basic procedure in which increasingly more specific information is gathered and analyzed in stages. In the Netherlands, a step wise protocol going from exploratory, qualification, and quantification stages is used [140]. Through each of the three stages, attention is focused both on exposures and disease, and decisions about possible causality are made at the end of each stage. Additionally, as with most cluster protocols, at the end of each stage a decision to progress with the investigation is made [129,141].

The primary objective of a cancer cluster investigation is to identify exposures that may be associated with excess cases in a workplace or location so that exposures can be controlled. When conducting a cluster investigation it is useful to consider a number of questions as the work proceeds through the various stages. The initial questions are: (1) is the incidence of disease really higher than normal and by how much? (2) is the exposure higher than normal or above allowable limits? and (3) is the link between exposure and cluster biologically plausible [142]? The stages of a cluster investigation allow for the collection of the necessary information to answer these questions and if these answers are affirmative then the investigation may progress to a full-scale epidemiological study attempting to determine the association between the exposure and increased risk.

Very detailed protocols for investigating reported cancer clusters have been published by health agencies and reviews have appeared in the peer reviewed literature [1,3-5,141,143-145]. In British Columbia, the protocol includes: Stage 1 – Initial contact and response, Stage 2 – Assessment, case evaluation and incidence evaluation, Stage 3 – Major feasibility study, and Stage 4 – Etiologic investigation [53]. In the State of Washington, their 18 page protocol has similar stages: (1) collect initial information and provide education and information to the informant, (2) assess the magnitude of the reported cluster, (3) determine utility and feasibility of further epidemiologic study, and (4) conduct detailed etiological investigation [3]. Other health departments have developed very similar systematic approaches to cluster investigations and all provide detailed procedures for data collection, analysis, and guidelines for making decisions at the end of each stage [141].

Analysis of Mission Memorial Hospital Laboratory Cancer Incidence Data

Events in the Mission Memorial Health Laboratory cancer cluster investigation

This investigation was conducted in response to concerns expressed by employees of the Mission Memorial Hospital (MMH) Laboratory that they were experiencing a high incidence of cancer. The investigation resulted in an initial report prepared by the Occupational Health & Safety Agency for Healthcare in BC (OHSAH) and released for comment in March, 2004 (Attachments 2 & 3). The associated presentation is included as Attachment 4. In addition, Attachments 5, 6 and 7 are supportive documents from the initial investigation. Subsequently a new breast cancer case was identified and errors in staffing levels were corrected. A re-analysis of the breast cancer incidence rate was completed in April, 2005 (Attachments 8 & 9) and a revised Draft Report was released in September, 2005. The revised Draft Report still did not address all of the concerns raised by the MMH Laboratory employees and resulted in a set of critical questions being posed which were presented to the Fraser Health Authority (FH) and OHSAH in November of 2005 (Attachment 10). The responses to these questions for which OHSAH was responsible were sent to FH and the Health Sciences Association (HSA) in January, 2006 (Attachment 11) and were presented at MMH on February 8th, 2006 to representatives of FH, HSA, the BC Nurses' Union (BCNU) and the Hospital Employees' Union (HEU). Some of the questions posed by the Laboratory employees were responded to by FH and are included as a separate document. This Final Report is therefore a compilation of the investigation of cancer incidence at the MMH Laboratory and the results of an extensive consultation process with the employer, labour representatives, and the individuals involved.

Cancer Cluster at the Mission Memorial Hospital Laboratory

The analysis of records and interviews of present MMH Laboratory employees initially identified 57 employees who were employed in the MMHL for periods exceeding one year over the last 30 years. Since the March 2004 report of the same title prepared by OHSAH, a new case of breast cancer in the workforce came to light, and along with it, a request to OHSAH to re-calculate the cancer rates. This final report includes the recalculation and takes into account the

additional person-years at risk that results from extending the analysis, as well as new information on the actual number of employees at risk.

Twelve cancer cases were reported among the subjects and were of the following types: breast (7), ovarian (1), liver (1), thyroid (1), lymphoma (1) and skin (1). Since the BC Cancer Agency's rates for "all cancers" does not include skin cancer, the subject reporting skin cancer was considered disease free for the statistical analysis. Thus, for the purpose of this analysis, the observed number of cancer cases in the study group was 11.

A total of 63 employees met the criteria for inclusion in the data analysis. Ten of 57 women in the study reported a cancer diagnosis whereas 1 of 6 men reported cancer. The mean age for all 63 employees was 46.9 years and the mean duration of follow-up was 15.4 years. The mean age of individuals reporting cancer (both breast and cancer at other sites) was higher than for those not reporting a diagnosis (Table 2).

Table 2: Age, gender and duration of follow-up by disease status

	No Cancer	Breast Cancer	Other Cancer	Total
Females	47 (74.6%)	7 (11.1%)	3 (4.8%)	57 (90.5%)
Males	5 (7.9%)	0	1 (1.6%)	6 (9.5%)
Mean Age (yrs)	45.7 (10.8)	53.4 (8.7)	51.7 (11.4)	46.9 (10.8)
Mean duration of follow-up (yrs)	15.1 (8.0)	17.7 (9.1)	14.6 (13.1)	15.4 (8.3)

To recalculate the incidence of cancer, we have used a new censor (closure) date of December 31st 2004 (versus August 31st, 2004) in order to include the most recent case. We asked the BC Cancer Agency (BCCA) to provide a data linkage for these 63 employees to ensure that there were no unreported cancer cases within this group. This information was not be available until August of 2005 and the possibility of an unknown case was low, we recalculated the rates using the numbers stated above (ie. 11 cases of cancer). That is, we have assumed no additional cases.

The expected number of cancers, adjusted for age and calendar year, for all 63 employees in the study was 2.3. For females only, the expected number of breast cancers was 0.8 and for all cancers it was 2.2. These expected cancer cases reflect the number of cases that would have occurred if the cohort of individuals (total employees or female employees) experienced the

same rate of cancer as the BC population. The computation of expected numbers of cases is adjusted for both the age of each individual as well as the calendar years that they were at risk. The findings from the statistical analyses are presented in Table 3.

Table 3: Observed and expected cases and age/calendar-year adjusted standardized incidence ratios (SIRs) for breast cancer (females only) and all cancers.

Cause	Person-years	Number of subjects	Expected cancers	Observed cancers	Standard Incidence Ratio	95% Confidence Intervals
Breast Cancer (females)	856.28	57	0.83	7	8.43	3.39 – 17.38
All cancers (females only)	856.28	57	2.18	10	4.59	2.20 – 8.44
All cancers (all subjects)	973.49	63	2.34	11	4.70	2.35 – 8.41

Data Presented as frequency, mean(standard deviation)

A finding of a SIR of 8.4 for breast cancer with 95 percent confidence intervals exceeding 1.0 indicates that the expected number of breast cancers was significantly elevated. The SIR of 8.4 indicates that the women in the MMH Laboratory were experiencing breast cancer incidence at approximately eight times the rate than women in the BC population. The 95 percent confidence intervals suggest that, the true SIR (since this is just a statistical approximation) was expected to be between 3 and 17 with 95 percent certainty. Therefore, statistically speaking, this is a true cluster of breast cancer cases that exceeds what is expected among women in BC. Similarly, the standard incidence rates for all cancers in both men and women were significantly elevated as compared to the rates in BC. However, given the large proportion of cancers that were of the breast, the excess in the total cancer SIRs was driven by the high number of reported breast cancers in the employee cohort.

Cox proportional hazard modeling showed that the variables Age at start of work at MMH Laboratory, Job Position (Technician vs. Aid, Clerk or ECG), and Job Status (Part time vs. Full Time) were not related to the hazard rate. The hazard rate is defined as the probability per time unit that a person who has not developed cancer to the beginning of the respective interval will develop cancer in that interval (Table 4). This is a very important finding. It suggests that there is

no significantly increased risk for women by job position or by job status and it means that women who started working in the MMH Laboratory at an older age are at a slightly increased (though non-significant) risk of developing breast cancer than younger women working in the laboratory.

Table 4: Hazard ratios and 95% confidence intervals (CIs) of breast cancer in relation to age at start of work at MMHL, position and occupational exposure at MMHL

Variables	n	Hazard Ratio	95% CI	p-value *
Age at start work (yrs)	57	1.07	0.95 – 1.21	0.264
Occupational exposure (yrs)	57	1.03	0.92 – 1.15	0.581
Position				
Aid, clerk or ECG technician	26	1.00		
Technician	31	4.24	0.36 – 49.38	0.249

* **p-value was derived from Cox proportional hazards model with age at start work and year of occupational exposure as a continuous variable and position as categorical variable.**

Field Investigations: Potential Exposures to Potentially Carcinogenic Substances or Physical Agents

The walk-through investigation was conducted in August 2003 and included a review of the current procedures that may result in employee exposures to chemical or physical agents. Questions were asked about past practices and exposures to gain an understanding about how exposures may have changed over the years.

Key points from the walkthrough are provided below:

- Current chemical exposures are minimal because liquid volumes are small and handling is often minimized through the use of "lock and load" systems

- Exposures to physical agents, such as ionizing radiation and electromagnetic fields appears to not be excessive (heat and noise exposures were also minimal). In September of 2004, Radiation Protection Services (BCCDC), completed an assessment of radiation exposure in the laboratory, concluding that "the exposures measured in the Mission Memorial Laboratory Area are typical natural background and that the X–ray facility is not contributing to this natural background…this natural background radiation would not contribute measurably to increased cancer risk." (Attachment 6)

- Past exposures were likely much higher as a number of procedures have been modified due to technological advances

    - A major change was in the preservation of tissue samples, tissue staining, and glucose measurement. These procedures, in the past, required open use of solvents and reagents which included formalin, xylene, and *o*-toluidine. Most of these procedures were performed in a separate area of the laboratory, which was removed when the procedures were modified. It should be noted that *o*-toluidine, which was discussed in the literature review, is a rat mammary carcinogen, and formaldehyde (the major component in formalin) is a known human carcinogen.

    - Other areas of the laboratory also were renovated due to changes in laboratory procedures. Remnants of a local exhaust ventilation system are present in one area where open chemicals were once mixed and dispensed.

- Poor indoor air quality was a common complaint in the past but appears to be less of a problem currently. An incinerator at the hospital was a source of very odorous and potentially hazardous compounds (likely acid gases and possible combustion products of PVC (monomers of vinyl chloride) and other plastics (halogenated organics)).

Previous air quality studies have been performed at MMH Laboratory; however investigators did not have access to the historical findings. In discussions with occupational health and safety professionals at FH, it was mentioned that previous studies were standard IAQ surveys and all measured concentrations of air contaminants were below regulated limits.

Conclusions

Summary

- The incidence of **breast** cancer among MMH Laboratory employees (SIR=8.4) statistically exceeds the expected incidence rate of breast cancer among women. Therefore this is a true cluster of breast cancer cases.

- We conclude, based on a proportional hazards analysis, that this increase is not statistically related to age at start of work or duration of exposure. The risk of breast cancer by job

position (technician vs. aid or clerk), is elevated but this increase is not statistically significant.

- On observation and literature review, no current occupational chemical exposures, or records of past occupational exposures were found that might relate working in the MMH laboratory environment to elevated breast cancer risk, or cancer in general. No significant findings were found during radiation testing in the laboratory, or on basic air quality testing.

- We conclude that this investigation be closed and an update to the analysis conducted in five years time. Should a larger cohort study be conducted that suggests an increase in breast cancer in laboratory workers, or if a hypothesis is generated based on new scientific knowledge, the concerns of the employees of MMH laboratory should be reviewed at that time.

In our study we did not gather personal information pertaining to known risk factors for breast cancer. The reason for not gathering this information was that this is a preliminary epidemiological study and information on risk factors is difficult to interpret without a comparison population where the prevalence of risk factors is available. For example, in our study if we had detailed information about reproductive factors, family history of breast cancer, socioeconomic factors, alcohol consumption, physical exercise, and obesity, we would only be able to compare the prevalence of those factors with those within the general population. Thus, such data would provide clues as to the possible reasons for the elevated risk – if the prevalence of these risk factors were the same as the general population it would suggest that occupational factor(s) predominate. Only a full-scale etiologic investigation would have the capability of clearly identifying occupational factors as attributable to the increased breast cancer risk.

A full-scale epidemiologic study is not an appropriate action to take despite the increased rates of cancer MMH Laboratory employees have experienced. The major goal of cluster investigations is to identify risk factors so that action can be taken to reduce exposures and risk. Air quality studies and reviews of procedures indicate that current exposures to carcinogens are minimal. Past exposures to chemicals like *o*-toluidine may have resulted in some increased risk for employees, but these exposures appear to have been eliminated.

Another issue that discourages a major epidemiologic investigation pertains to the statistics of clusters themselves. Cluster research has shown that elevated rates occur by chance at some geographic locations and times. In fact, clusters always occur and it is a statistical phenomenon – even when there is no causal factor that is responsible for the increased incidence (this is why so few cluster investigations uncover any new risk factors). So, if we look around at many geographic areas and times we will find some clusters; if a specific cluster is related to statistics and not an etiologic agent, it is most likely that in the next time period at this location the rate will not be significantly elevated. Thus, it would be very prudent to continue to evaluate the incidence of breast cancer in MMH Laboratory employees to see if the rate comes closer to what is expected.

In summary, this study confirmed that the perceived cluster was an observed cluster and that MMH Laboratory employees were experiencing an elevated rate of breast cancer. The factors associated with this increased incidence could not be determined but may have been due to: (1) a cluster of reproductive and other known, non-occupational, risk factors, (2) past exposures to chemical carcinogens and less likely to ionizing radiation, and (3) a statistical anomaly.

Recommendations

Our recommendations for action to be considered are:

(1) provide education to all employees about risk factors for breast cancer and the importance of self exams and mammography, with assistance provided to ensure access to mammography if needed;

(2) continue to collect information on the incidence of breast and all cancers in the future so that standardized incidence ratios (SIRs) can be re-calculated in five years time;

(3) a new investigation can be considered at a future time if larger cohort studies suggest a link between breast cancer and hospital work, or laboratory work in particular, and/or if new scientific knowledge allows for a hypothesis on work-related causation to be generated for testing; and .

(4) Every effort should continue to be made, in this and all workplaces, to ensure that workplaces remain as safe and free of carcinogenic exposures as possible, and that the workforce is able to pursue safe and healthy choices in all aspects of their lives.

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Attachment 1

Potential Exposures to Potentially Carcinogenic Substances or Physical Agents
August 2003

Field Investigations: Potential Exposures to Potentially Carcinogenic Substances or Physical Agents

The walk-through investigation was conducted in August 2003 and included a review of the current procedures that may result in employee exposures to chemical or physical agents. Questions were asked about past practices and exposures to gain an understanding about how exposures may have changed over the years.

Key points from the walkthrough are provided below:

- Current chemical exposures are minimal because liquid volumes are small and handling is often minimized through the use of "lock and load" systems
- Exposures to physical agents, such as ionizing radiation and electromagnetic fields appears to not be excessive (heat and noise exposures were also minimal)
- Past exposures were likely much higher as a number of procedures have been modified due to technological advances
    - A major change was in the preservation of tissue samples, tissue staining, and glucose measurement. These procedures, in the past, required open use of solvents and reagents which included formalin, xylene, and *o*-toluidine. Most of these procedures were performed in a separate area of the laboratory, which was removed when the procedures were modified. It should be noted that *o*-toluidine, which was discussed in the literature review, is a rat mammary carcinogen, and formaldehyde (the major component in formalin) is a known human carcinogen.
    - Other areas of the laboratory also were renovated due to changes in laboratory procedures. Remnants of a local exhaust ventilation system are present in one area where open chemicals were once mixed and dispensed.
- Poor indoor air quality was a common complaint in the past but appears to be less of a problem currently. An incinerator at the hospital was a source of very odourous and potentially toxic compounds (likely acid gases and possible combustion products of PVC (monomers of vinyl chloride) and other plastics (halogenated organics)).
- Previous air quality studies have been performed at MMHL, however investigators did not have access to the findings. In discussions with occupational health and safety professionals at FHA, it was mentioned that all measured concentrations of air contaminants were below regulated limits.

Attachment 2

An Investigation of a Cancer Cluster within the Mission Memorial Hospital Laboratory March 2004

An Investigation of a Cancer Cluster within the Mission Memorial Hospital Laboratory

March 2004

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Abstract

An excess in the number of cases of cancer was suspected by employees of the Mission Memorial Hospital Laboratory and this investigation was conducted in response to the above concern. The study had three parts, an epidemiologic cluster analysis, a comprehensive review of the literature on breast cancer risk factors and the analysis of clusters, and an exposure investigation. A total of 57 individuals were identified as having worked in the laboratory between January 1, 1970 and August 31, 2003. Information on health status and diagnoses of cancer was obtained through personal interviews with employees. Ten employees reported a cancer diagnosis, of which 6 were breast cancer. A total of 704 person-years of observation were available for the data analysis after the exclusion of subjects because of diagnoses of cancer prior to start of employment (n=1) and lost to follow-up (n=10). Based on the age and calendar-year adjusted rates for the BC population, the expected number of breast cancer cases in the women was 0.56, and the expected number of all cancers for all employees was 1.51. The Standard Incidence Ratios (SIR), which are the observed number of cases divided by the expected number, were 10.7 for breast cancer in women, and 6.6 for all cancers in both men and women. The 95 percent confidence intervals indicate both findings were significant. A walk-through survey of the laboratory did not identify any potentially hazardous exposures. Recommendations include a comprehensive assessment of all potential exposures to chemicals and physical agents, continuing to collect epidemiological information to determine temporal trends in the SIR, providing information on breast cancer risks to employees, and collecting information on known risk factors for breast cancer and confirming cancer diagnoses through linkage with the BC Cancer Agency's registry.

Introduction

The Occupational Health and Safety Agency for Healthcare (OHSAH) was invited by the Fraser Health Authority (FHA) to investigate concerns of a greater than expected number of cancer cases in the Mission Memorial Hospital Laboratory (MMHL). In addition to the seemingly high total number of cancer cases, a large proportion were the same type (breast cancer) thus further highlighting the need for an investigation. Occupational health professionals from FHA had completed some exploratory work on the project but felt they needed the help of outside experts to resolve the issues. OHSAH conducted a preliminary cluster investigation which is the focus of this report. Dr. Philip Bigelow, a senior scientist at OHSAH, led the investigation and team members included Dr. Annalee Yassi, Rosemary Nemanishen, Dr. Shicheng Yu and William So Yiu Ting. Assistance was also obtained from Dr. Nhu Lee of the British Columbia (BC) Cancer Agency and Dr. Martha Vela Acosta of the Department of Environmental and Radiological Health Sciences at Colorado State University.

Cancer clusters are the occurrences of greater numbers of the same type of cancer, or all cancers, within a geographic location over a specified period of time. The purpose of a cancer cluster investigation is to determine if the observed number of cases is higher than expected. If the observed number is higher, the study should provide information that may help to reduce or eliminate exposures that may be associated with the increased risk. Cancer cluster investigations are often conducted by health agencies and this investigation followed general guidelines recommended by the BC Cancer Agency and public health departments in other jurisdictions across North America (Schulte, Ehrenberg et al. 1987; Caldwell 1990; Cartwright 1999; WSDOH 2001). Prior to the investigation, an explanatory meeting was held at Mission Memorial Hospital to discuss the incidence of cancer at MMHL and the protocol for the investigation. Details of the protocol used during the investigation are provided below.

Methods

The specific aim of this study was to provide a thorough determination if an excess in the number of cancer cases had occurred in the Mission Memorial Hospital Laboratory (MMHL) and to provide information regarding the possibility that a work-related factor was involved. More importantly, the goal was to ensure that current workplace conditions and exposures are not at all likely to result in an increased risk of cancer for employees.

The BC Cancer Agency, as well as other health agencies, have adopted standard protocols for investigating clusters. The methods used in our study followed these standard procedures and included determining if an excess number of cancers was reported, a literature review on the risk factors for the specific cancer types, assessing the potential for occupational exposures to potentially carcinogenic physical agents or substances, and determining the feasibility of further epidemiology studies. Our study was divided into three components as listed below.

1) Analysis of Cancer Incidence Data: Epidemiology and Statistics

Since the concern pertained to employees in the MMHL, only employees who worked in the Laboratory were included in the study. Using data from the Human Resources Department at Mission Memorial Hospital, all employees who were employed in the Laboratory over the past 33 years (January 1970 to August 2003) were identified and this information was provided to an occupational health professional at Fraser Health. A total of 57 individuals were identified and the following information was entered into a computer spreadsheet: date of birth, dates of employment at the lab, job title, full or part time employment status, gender, and other details pertaining to work at the lab and hospital. A health professional (Registered Nurse) from Fraser Health attempted to contact all 57 individuals (in person or by telephone) to gather information on whether or not they had a diagnosis of cancer of any type. For individuals who reported a cancer diagnosis, information on the diagnosis date, type and site of cancer was obtained. Data for all 57 individuals, without personal identifiers, were entered into a spreadsheet and provided to OHSAH.

The statistical analysis was conducted two ways. In one, the person-years of observation was defined as being from the start date of employment at MMHL to the end date of employment. In the second analysis, the person-years of observation was defined as the time between the employee start date and the end of the follow up period (August 2003). In this report the latter analysis is provided, as it is the most appropriate for the study design that was used.[1]

Since a large proportion of the cases were classified as breast cancers, statistical analyses were conducted using rates of breast and total cancers obtained from the BC Cancer Agency. Rates for breast and total cancers for each year from 1970 to 2002, grouped by 5 year age intervals, were used to calculate the expected number of cases in the study group. The expected number of cases is the number of cases expected in the Laboratory if the rate was the same as the rate in BC adjusted for age and calendar year.[2] The expected number of cases was computed by multiplying the population (person-years of observation) within each specific age range and year by the rate of breast or total cancers for the same age interval and year. The results of these computations were summed across all the age and year categories to get the total number of expected cases. Computations and statistical analyses were conducted using Excel and SPSS software.

[1] In many occupational cohort studies, when subjects leave employment their health status at that time is known and their end date of employment is used in the computation of person-years of observation. In this study, we contacted all study subjects from August to November, 2003 to determine their health status.

[2] The risk of developing breast cancer was different in 1980 as compared to today. Additionally, age is a major risk factor for all cancers (including breast cancer). Therefore, crude incidence rates may be misleading when comparing regions or time periods where the age of the populations differ from one region to another or from one time period to another. In this study, the expected number of breast and total cancers was adjusted for age and calendar year and this provides the most accurate comparison of rates for this study.

The observed number of cases was divided by the expected number of breast cancer and total cancer cases to determine the Standard Incidence Ratios (SIR). A SIR exceeding 1.0 indicates the observed number is higher than expected. Confidence intervals are used to assess variation in the SIR and 95% Poisson confidence intervals were calculated using the procedure suggested by Breslow (Breslow 1987).

2) Field Investigations – Potential Exposures to Potentially Carcinogenic Substances or Physical Agents

Prior to this investigation, work had been conducted by occupational health professionals at Fraser Health to determine the adequacy of procedures to control exposures to chemicals in the laboratory and to ensure exposures did not exceed government or consensus standards. Investigations also focused on potential sources of chemical exposures resulting from work tasks that are typically performed by laboratory personnel. An additional study included reviewing past renovations of the laboratory in hopes of identifying unusual sources of indoor air contaminants.

In August of 2003, as part of OHSAH's investigation, a walkthrough survey of the laboratory was completed. Typical work procedures were reviewed to assess the potential for exposures to hazardous agents. Employees in the laboratory provided information on historical procedures as well as an indication of the general levels of exposure to air contaminants.

3) Literature Review

The investigation and response to cancer cluster reports is exceedingly complex and the report includes brief literature reviews on risk factors for breast cancer, exposures in laboratories, and epidemiology of cancer clusters. This information is provided to help interpret the study findings and provide guidance in deciding whether further study is warranted.

Results and Discussion

The literature review is presented first as it provides a background for interpreting the findings from both the epidemiologic analysis and the field surveys. The literature review of breast cancer highlights the multifactorial nature of disease causation and the difficulties in determining the role of environmental and occupational exposures as causal factors. There is a substantial body of literature on cancer cluster investigations and a brief review is provided. Finally, the findings of the statistical analysis are provided and discussed in relation to findings from other studies.

Literature Review: Breast Cancer Risk Factors and the Role of Occupational and Environmental Exposures

Breast cancer. Canada has one of the highest rates of breast cancer incidence and the age standardized rate in 1995 exceeded 225 per 100,000 women aged 40 and over (Jacobzone

2002). Breast cancer is the most frequently diagnosed cancer in Canadian women and it accounts for over 30% of new cancer cases per year (NCIC 1999). It is estimated that one in nine women in Canada will develop the disease in their lifetime (DeBruin and Josephy 2002). Breast cancer mortality increased steadily from the 1960s until the early 1980s when the rates declined in most countries including Canada (Parkin, Bray et al. 2001; Parkin, Bray et al. 2001). These declining mortality rates are thought to be related to improved screening resulting in earlier detection and improved treatment.

Age is major risk factor for breast cancer and Table 1 shows the increased likelihood of a woman developing breast cancer in the next five years at various ages (PPHB 2004). In addition to age, many correlates of risk for breast cancer have been identified and there are a constellation of hormone-related reproductive factors that predominate. Factors known to confer higher risk include younger age at menarche, older age at menopause, nulliparous, and older at first live birth (Davis, Axelrod et al. 1997). Higher parity, longer lactation, and bilateral ovariectomy have been found to be protective (Davis, Axelrod et al. 1997; Kreiger, Sloan et al. 1999). Using data from large population-based surveys in the United States (US), investigators calculated that 41% of breast cancer risk was explained by nulliparity, later childbearing, higher income, and family history of breast cancer (Madigan, Ziegler et al. 1995). Other risk factors for breast cancer include a history of certain types of benign breast disease as well as high levels of radiation exposure to the chest (medical x-rays) (PPHB 2004). Despite the many studies that have been conducted, additional factors, likely modest in magnitude, remain to be discovered. Interestingly, in 76% of women who develop breast cancer, age is the only identifiable risk factor (Halls 2003).

Table 1.[3] Probability of developing breast cancer in the next five years.

Age	Breast cancer per 1,000 women
30	1.5
35	2.6
40	4.8
45	7.8
50	9.2
55	10.6
60	12.9
65	14.3
70	15.4
80	15.5

Epidemiological and animal studies consistently show elevated risk of breast cancer with factors that increase exposure to estradiol, progesterone, and other hormones (Kreiger, Sloan et al. 1999; Medina 2004; Recchia, Vivacqua et al. 2004; Zeleniuch-Jacquotte,

[3] From PPHB (2004). Breast Cancer in Canada. online at: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/updates/breast-99_e.html, Population and Public Health Branch, Health Canada, Ottawa, Canada. **2004**.

Shore et al. 2004). Risk factors such as alcohol consumption, weight gain after menopause, low pre-menopausal body mass index, and lack of physical exercise are believed to be associated with exposure to reproductive hormones (Hamajima, Hirose et al. 2002; McTiernan, Rajan et al. 2003; Patel, Press et al. 2003; Yang, Bernstein et al. 2003). Pharmaceutical hormones appear to have a similar effect and there is evidence that women exposed to diethylstilbestrol during pregnancy had increased risks for breast cancer (Laitman 2002; Schulmeister 2003). For oral contraceptives, recent use, not long term exposure, has been associated with an increased risk (Burkman 1999; Deligeoroglou, Michailidis et al. 2003). Similarly, recent use of hormone replacement therapy has been shown to increase the relative risk of breast cancer, whereas women who stopped over 5 years ago are not at significantly elevated risk (Vassilopoulou-Sellin 2003).

In epidemiological studies higher socioeconomic status, as measured by income and education level, are consistently associated with elevated breast cancer risk (Mackillop, Zhang-Salomons et al. 2000; Gordon 2003). Although some of this association may be due to a clustering of reproductive risk factors in higher socioeconomic status women, the effect is still significant even after controlling for parity, age at first child and other common reproductive factors (Brody and Rudel 2003). Diet has been well studied but epidemiological investigations have yet to identify foods that significantly increase or decrease breast cancer risk (Higginbotham, Zhang et al. 2004). It is hypothesized that dietary factors may modulate hormone levels so a number of investigations have focused on foods high in phytoestrogens (Hargreaves, Potten et al. 1999; Sarkar and Li 2003) (partial estrogen agonists) or containing other endocrine active components (Brody and Rudel 2003).

Studies of occupational and environmental factors. Animal studies have provided important information in understanding mechanisms of the development of breast cancer and in the identification of agents that may increase breast cancer risk. A comprehensive review of chemical carcinogenesis in general is beyond the scope of this paper, but it should be noted that all cancer causing agents, physical or chemical, will also have the potential to initiate or promote breast cancer. A good example is ionizing radiation which is know to cause cancer at multiple sites; based on human epidemiological studies, it is one of the few occupational or environmental exposures that is a known cause of breast cancer (Land, Tokunaga et al. 2003; Ron 2003).

Studies indicate that estrogen receptor (ER) alpha mediates the breast cancer promoting effects of estrogen. Estradiol binds to ER alpha and induces estrogen receptor-mediated transcription, DNA synthesis, cell division, and cell proliferation which is associated with an increase in errors in DNA transcription. Estrogen and progesterone, both essential for mammary gland growth and function, cause cell proliferation and may be procarcinogenic (DeBruin and Josephy 2002). Both estrogen and progesterone are cytotoxic as they interact with specific receptor proteins in the cell nucleus. Recent research provides evidence that estrogens can be metabolically activated to genotoxic compounds that induce oncogenic mutations (Yue, Santen et al. 2003). Thus, the carcinogenicity of estrogens, as well as their action in increasing susceptibility, may be

related to a receptor mediated stimulation of cellular proliferation. Human studies have provided some evidence to support this hypothesis (Wang, Allen et al. 2000). Even without a complete understanding of the mechanism, it is clear that lifetime exposure to estrogen and other hormones explains many identified risk factors for breast cancer.

Cells within the breast are not fully differentiated until they are induced by hormonal stimuli at the woman's first pregnancy and lactation. Thus, breast cells are more susceptible to the effects of carcinogens while the breast is not fully developed. Additionally, the breast cells are vulnerable to genotoxic agents during pregnancy as there is rapid proliferation of cells (Russo and Russo 1996; Russo and Russo 1997). This explanation of the susceptibility of mammary cells to carcinogens provides a framework for understanding the increased risk of breast cancer in humans in relation to reproductive events as well as after exposure to mammary carcinogens. It has been hypothesized that, because the breast is very susceptible to carcinogen exposures up until the first full-term pregnancy, there may be an interaction of age (a known risk factor) and the risk associated with exposures to chemicals (Brody and Rudel 2003).

Despite the complex mechanisms and interactions between chemical exposures and hormones, animal studies have clearly identified numerous mammary carcinogens through standard cancer bioassays. The US National Toxicology Program (NTP) has tested over 500 chemicals and identified 42 as causing mammary tumors (Bennett and Davis 2002). The human evidence for identifying chemicals causing breast cancer is more scant and of the 42 chemicals cited above, only four are classified as human carcinogens: benzene, 1,3-butadiene, ethylene oxide, and C I acid red 114. Also, it should be noted that epidemiology studies of these compounds have shown exposed employees at higher risk of cancer, but not specifically breast cancer. Mammary carcinogens that may be associated with exposures in chemical and medical laboratories are presented in Table 2 below.

Table 2.[4] Chemicals tested by NTP that produce mammary tumors in experimental animals

Chemical	Use
Acronycine	Pharmaceuticals
Benzene	Gasoline, solvent
2,2-bis(bromomethyl)- 1,3-propanediol	Flame retardant
1,3-Butadiene	Auto exhaust, rubber manufacture, gasoline
C,1 acid red 114	Dye for silk, jute, wool, leather
C,1 basic red 9 monohydrochloride	Dye for textiles, leather, paper, biological stain
2-Chloroacetophenone	Flame retardant
Chloroprene	Used in neoprene manufacture
Clonitralid	Molluskicide
Cytembene	Pharmaceuticals
2,4-Diaminotoluene	Intermediate in dye synthesis
1,2-Dibromo-3-chloropropane	Soil fumigant, pesticide
1,2-Dibromoethane	Soil fumigant, lead scavenger in gasoline
1,2-Dibromo-1-propanol	Flame retardant
1,1-Dichloroethane	Solvent
1,2-Dichloroethane	Solvent, chemical intermediate in insecticide formulations, gasoline
1,2-Dichloropropane (propylene dichloride)	Chemical intermediate, solvent in dry cleaning fluids, fumigant
Dichlorvos	Pesticide
1,2-Dimethoxybenzidine dihydrochloride	Dye intermediate
3,3-Dimethylbenzidine dihydrochloride	Dye intermediate
2,4-Dinitrotoluene	Dye intermediate, explosives, propellants
Ethylene oxide	Sterilizing gas for medical equipment
Furosemide	Pharmaceuticals
Glycidol	Stabilizer in vinyl polymers, intermediate in pesticides and fragrances
Hydrazobenzene	Dye intermediate, tobacco pesticides, motor oil
Isophosphamide	Pharmaceuticals
Indium phosphide	Microelectronics, semiconductors, injection lasers, diodes
Isoprene	By-product of ethylene production
Methylene chloride	Solvent, furniture stripper, adhesives
Methyleugenol	Food additive, flavoring, also naturally occurring
Nithiazide	Antiprotozoal compound
5-Nitroacenaphthene	Research chemical
Nitrofurazone	Antibiotic
Nitromethane	Rocket and engine fuel, solvent, mining explosive
Ochratoxin A	Mycotoxin
Phenesterin	Pharmaceuticals
Procarbazine hydrochloride	Pharmaceuticals
Reserpine	Pharmaceuticals
Sulfallate	Herbicide
2,4- and 2,6-Toluene diisocyanate	Used in manufacture of flexible polyurethane foams
o-Toluidine hydrochloride	Dye intermediate
1,2,3-Trichloropropane	Chemical intermediate, former solvent and paint remover

[4] From Bennett, L. M. and B. J. Davis (2002). "Identification of mammary carcinogens in rodent bioassays." Environ Mol Mutagen **39**(2-3): 150-7.

Both animal and human studies show that the relationships between hormonal factors and mammary carcinogens is complex. Treatment of animals with ovarian, placental, pituitary, and thyroid hormones modulates the tumorgenic responses (Russo and Russo 1998). The situation is further complicated with exposures to chemicals that are members of a class of hormonally active chemicals, sometimes referred to as endocrine active, endocrine disruptors, or estrogenic compounds. The hypothesis is that exposure increases estrogen-like responses of cell proliferation that increase cancer risk. There is also a concern that these endocrine active compounds can act in an additive manner to produce effects (Charles, Gennings et al. 2002; Brody and Rudel 2003).

Chemicals, including some pesticides, also can act as co-carcinogens or tumor promoters (Bounias 2003). A good example of a breast cancer promoter in experimental animals is dichlorodiphenyltrichloroethane (DDT). Experimental animals fed a known mammary carcinogen, and then given DDT, developed breast tumors earlier than when the carcinogen was given alone; however, when DDT was given alone, it did not induce breast tumors in these animals (Snedeker 1997). The human evidence of DDT's effects as a promoter is more equivocal, although a recent study reported significantly elevated mean levels of serum DDT and hexachlorobenzene (HCB) in breast cancer patients as compared to controls (Charlier, Albert et al. 2003). Other organochlorine compounds have been implicated as being associated with an increased risk of breast cancer. The hypothesis is that this group of compounds possess estrogenic activity. However, both the hypothesis and the magnitude of any possible effect on human risk of breast cancer is controversial. Recent reviews suggest that the estrogenic contribution of organochlorine compounds is small in view of the presence of natural hormone and antihormone mimics in our diet (Safe and Zacharewski 1997; DeBruin and Josephy 2002). Other endocrine active compounds, such as alkyl phenols and phthalates are still under investigation (Sonnenschein and Soto 1998).

Studies of breast cancer risk in working populations have not provided strong evidence of causal links between specific exposures and increased risk. However, there is evidence for positive associations of several occupations with increase breast cancer risk (Morton 1995; Goldberg and Labreche 1996; Band, Le et al. 2000). The study by Band et al. (2000) was conducted in British Columbia and found significantly higher breast cancer risks (1) among *pre-menopausal* women in electronic data-processing operators; barbers and hairdressers; in sales and material processing occupations; and in the food, clothing, chemical and transportation industries; (2) among *post-menopausal* women in school teaching; in medicine, health, and nursing occupations; in laundry and dry-cleaning occupations; and in the aircraft and automotive, including gasoline service station, industries. Several significant associations were also seen in the combined group of pre- and post-menopausal women, particularly in crop farmers and in fruit and vegetable farming, publishing and printing, and motor vehicle repair industries. The authors suggested that there was excess breast cancer risk in a number of occupations and industries, notably those that entail exposure to solvents and pesticides (Band, Le et al. 2000).

Shiftwork causes employees to have exposure to light at night and may increase the risk of cancer by suppressing the normal nocturnal production of melatonin by the pineal gland. Melatonin, is not only a hormone that has antiproliferative effects which protect against the development of cancer (Schernhammer, Laden et al. 2003), but it also modulates estrogen release from the ovaries. When nocturnal melatonin production is suppressed, the direct antiproliferative effects are reduced and estrogen release may be increased (Davis, Mirick et al. 2001). In a study of female nurses in a large prospective health investigation, women working a rotating night shift at least three nights per month for 15 or more years were at an increased the risk of colorectal cancer (Schernhammer, Laden et al. 2003). A recent population-based, case-control study found that graveyard shiftwork was associated with increased breast cancer risk (OR = 1.6; 95% CI = 1.0 to 2.5), with a trend of increased risk with increasing years and with more hours per week of graveyard shiftwork (Davis, Mirick et al. 2001).

Clinical laboratory workers have the potential for exposure to a variety of chemical, biological, as well as physical agents (Weaver 1997; Tompa, Major et al. 1999; Bigelow 2000). Despite the fact that chemical and clinical laboratories employ many women (over 1 million in the US), few studies have examined the possible adverse effects of exposures. Burnett et al. (1999) conducted a study to determine if laboratory workers in the US experienced higher cancer mortality rates than those in other occupations. They found clinical laboratory workers had higher proportionate cancer mortality ratios overall (for all cancers) as well as for breast cancer. The proportionate mortality ratios for leukemia were also significantly elevated for clinical laboratory workers (Burnett, Robinson et al. 1999). The authors suggest that the elevated risks for lymphatic and hematopoietic neoplasms may have been associated with occupational exposures.

With the exception of a few studies that have identified very high occupational exposures to carcinogenic compounds as causal factors in breast cancer, most investigations have not been able to clearly determine occupational risk factors (Goldberg and Labreche 1996). The reasons for the failure to identify specific chemicals or physical agents include not only the complex nature of the initiation, promotion, and development of breast cancer, but also the presence of many potential confounding risk factors. Additionally, there appear to be numerous, but so far unidentified, risk factors that the issue of confounding becomes even more salient. Little is known about the interaction of known risk factors on the magnitude of increase in breast cancer risk and even less is known about the possible synergistic, additive, or antagonistic effects of multiple chemical exposures.

The strength of already known breast cancer risk factors makes the identification of occupational risk factors very difficult. When examining the role of these major risk factors, it has been estimated that 41 percent of breast cancer risk is attributable to later childbearing, nulliparity, higher income, and family history of breast cancer (Madigan, Ziegler et al. 1995). Studies that have focused on genetic variation have estimated that less that 10 percent of cases are due to gene mutations in the breast cancer genes *BRCA1* and *BRCA2* (Claus, Schildkraut et al. 1996). Diet, alcohol consumption, physical activity, body mass index, other reproductive factors, high chest radiation exposure, and

exposure to pharmaceutical hormones all account for some risk in the development of breast cancer. In occupational studies, if the likelihood of exposure to these known breast cancer risk factors is increased in an occupational group, an association between the occupation and increased breast cancer risk will be observed. Additionally, the presence of powerful risk factors may mask the effect of an exposure that is truly increasing breast cancer risk.

Traditional epidemiological methods are typically not able to identify occupational risk factors for breast cancer at the levels of exposure seen in modern industry in Canada or the US. Newer methods that include the use of biological markers of exposure and incorporating gene-environment interactions have shown promise. These methods are better able to uncover subtle differences in risk and also provide an understanding of the underlying mechanisms. An example of these cutting edge techniques is the measurement of the aromatic amine, *o*-toluidine, a rat mammary carcinogen, in human milk samples from mothers. The presence of this chemical indicates that the ductal epithelial cells of the breast are exposed to this carcinogen (DeBruin, Pawliszyn et al. 1999). The use of biomarkers and gene-environment interactions have elucidated the complex associations of smoking, polymorphisms of drug metabolizing enzymes, and reproductive factors in breast cancer risk (DeBruin and Josephy 2002). These techniques have not been rigorously applied in studies involving occupational exposures and breast cancer but their use has been advocated (DeBruin and Josephy 2002; Ward, Schulte et al. 2003).

Literature Review: Cancer Clusters

Incidence rates of breast cancer, and all cancers, vary over time and geography and a cancer cluster is generally defined as the occurrence of a greater than expected number of cases of a particular cancer within a group of people, a geographic area, or a period of time. Studying and describing these spatial and temporal trends have provided clues for identifying previously undiscovered causes of cancer. In fact, the first causal relationship between an occupational exposure and cancer was uncovered as the result of a cluster investigation of scrotal skin cancer among young chimney sweeps in London (Pott 1996). Epidemiologists, the scientists most often leading the investigation of clusters, generally encounter clusters because of reports or through discovery from organized analyses of large databases (Kheifets 1993). Although the methods of analysis differ slightly depending on how the cluster is first identified, in both cases the results are difficult to interpret and drawing definitive conclusions is often not possible.

As was discussed in the section on breast cancer risk factors, some variation in breast cancer risk can be explained by the population distribution of known risk factors such as parity, age at first child and other reproductive factors (Robbins, Brescianini et al. 1997). In fact, grouping of reproductive risk factors and socioeconomic status play a major role in the findings of positive associations between white collar occupations and increased risk of breast cancer (Brody and Rudel 2003). However, regional patterns of increased and decreased breast cancer risk may reflect a complex aggregation of diverse factors which may include diet, demographics, lifestyle factors, and occupational and

environmental exposures. Gaining an understanding of these individual factors and their relationships is necessary to have a complete understanding of breast cancer risk in individuals and specific groups of women.

For breast cancer, clusters of relatively high incidence rates have been reported in areas of southern Alberta and British Columbia (NRC 2004). This type of variation by region is common and it is most often unclear whether or not the determinants of these differences are related to environmental, lifestyle, or other exposures. Even in populations that are well studied, such as in the Long Island, New York Breast Cancer Study Project (Wittenberg 1994; Gammon, Neugut et al. 2002), limitations in study design make the finding of significant environmental risk factors unlikely. In most investigations, biological data relating to occupational or environmental exposures is sparse or inadequate and other risk factors are not well controlled. Thus, even very extensive investigations of breast cancer clusters have high probabilities of failing to identify occupational or environmental risk factors (Timander and McLafferty 1998).

Breast cancer cluster investigations are often limited because of the effect of the very strong risk factors related to endogenous hormones that increase breast cancer risk. The question still remains: do exposures to hormone-mimicking chemicals or other chemical and physical agents also exert an effect? A multidisciplinary workshop, titled "Hormones, Hormone Metabolism, Environment, and Breast Cancer," convened by the National Action Plan on Breast Cancer, the US National Cancer Institute, Tulane University, and the U.S. Public Health Service's Office of Women's Health, in September 1995 discussed the complexity of factors, unresolved controversial issues, and the need for improved methodology to measure hormones and their metabolites (NCI 1997). As is the case with occupational studies of breast cancer, molecular as well as bioinformatic techniques were discussed as useful tools in gaining an understanding of the complex relationships between genes, individual factors, and the environment.

Investigating cancer clusters: Methods and limitations

The first of the modern cancer cluster reports began in the 1960s and the increasing number of reports spurred the development of investigation protocols. At a US National Cancer Institute conference on clusters, Dr. Langmuir advocated a simple approach: "The constructive approach to this situation, in my opinion, is not to develop highly refined statistical techniques to determine whether or not a certain cluster may have resulted by chance alone. But, rather to investigate each cluster as it is reported and see if additional associations of possible interest can be found. If none turn up, this is obviously a cold trail, and any good hunting dog will abandon it, and look for a better one. If the scent strengthens, then hot pursuit is in order" (Langmuir 1965).

Langmuir's advice for a simple approach did not deter the development of statistical models to resolve the issue of whether cancer cases were occurring independently or if they appeared to be related. A number of theoretical statistical methods have been developed and modified to detect clusters and to assess the statistical associations of interest. A detailed review of the theories underlying these sophisticated statistical

approaches is beyond the scope of this discussion and interested readers should consult articles describing specific statistical techniques as well as comprehensive reviews of the subject (Langmuir 1965; Schulte, Ehrenberg et al. 1987; Hanrahan, Mirkin et al. 1990; Hall, Lee et al. 1996; Kulldorff, Athas et al. 1998; Knorr-Held and Rasser 2000; Lawson 2000; Gangnon and Clayton 2001). Most of the models developed are useful when information is available on the observed cases in many discrete geographic locations and time intervals; the models then provide the likelihood of any one discrete location/time interval having a number of cases that is excessive. Thus, these techniques have most utility when there is routine monitoring of cases across large geographic areas (i.e., province-wide or Canada-wide surveillance programs).

The detection and analysis of cancer clusters most often is the responsibility of public health agencies such as local health departments, state or provincial health authorities, cancer registries, or national health agencies (Health Canada or the US Centers for Disease Control (CDC)). The Canadian Cancer Incidence Atlas is a recently developed national atlas that assesses the significance and spatial correlation of the age-standardized rates for 290 census divisions across the country (Semenciw, Le et al. 2000). The Atlas provides information about cancer incidence rates and is able to determine if cancer rates are significantly elevated in certain areas. As discussed previously, the Lower Mainland of BC is one area in which breast cancer incidence rates are significantly elevated as compared to the national average (NRC 2004).

When a cancer cluster is first reported, usually by concerned employees or citizens, the cluster is termed a *perceived cancer cluster*. If an investigation determines that the observed number of cases significantly exceeds the expected number it is termed an *observed cancer cluster*. If, after further investigation, a risk factor can be identified the cluster is called an *etiologic cancer cluster* (Aldrich and Sinks 2002). In investigating cancer clusters the goal is to determine if the cluster is real (observed cancer cluster); and, if it is real, to determine if it is or is not an etiologic cancer cluster. If the investigation uncovers an etiologic cancer cluster, efforts should be made to reduce/modify the causal factors (exposures) that are responsible for the increased risk.

Public concern pertaining to environmental exposures and cancer resulted in the reporting of many perceived cancer clusters over the past 20 years (Trumbo 2000; Siegrist, Cvetkovich et al. 2001). Public health authorities responded to these concerns by conducting investigations that varied in scope and cost. Considerable resources were allocated to cluster investigations and most did not identify etiologic cancer clusters. The US CDC, from 1961 to 1982 investigated 108 reported cancer clusters in 29 states and 5 foreign countries; no clear cause of cancer was determined for any of the reported clusters (Caldwell 1990). The Minnesota Department of Health (MDOH) investigated more than one thousand cancer clusters between 1984 and 1995 without identifying a particular cause in any (Garry, Jacobs et al. 1989). As a result of these many investigations, the MDOH developed a widely adopted systematic approach for cluster investigations (Bender 1987; Bender, Williams et al. 1990).

Cancer clusters also occur in the workplace and a number of the classic exposure-disease relationships arose from investigations of clusters. The determinations that polycyclic aromatic hydrocarbons, asbestos, and vinyl chloride monomer are human carcinogens were made though analyses of cancer clusters in workers where these products were manufactured or used (Lieben 1966; Lieben and Pistawka 1967; Pott 1996; Lewis and Rempala 2003). These etiologic clusters occurred before modern industrial hygiene controls were implemented and resulted from very high exposures to potent carcinogens. These early occupational cancer cluster investigations were effective in identifying and controlling large cancer risks that workers faced before the 1970s. Consequently, the role of occupational carcinogens in current clusters is more subtle than in the past and more difficult to detect.

In the US, the National Institute for Occupational Safety and Health (NIOSH), through its Health Hazards Evaluation Branch, is often called upon to investigate reported cancer clusters. In a review of 61 cancer clusters investigations that NIOSH completed between 1978 and 1984, a numerical excess of cases compared with expected numbers was found in 16 of the reported clusters (Schulte, Ehrenberg et al. 1987). In most of the reported clusters, no identified environmental exposure could be identified. In five of the 16 clusters there were exposures to potential carcinogens and the exposure-disease relationship was plausible (sufficient induction time and timing of exposure). Almost all of the investigations were limited by small numbers of cases, absence of complete personnel records, and other methodological and statistical issues that prevented the identification of specific causal occupational risk factors (Schulte, Ehrenberg et al. 1987).

In Canada there have been few published cancer cluster investigations that have identified a specific cause that was occupationally related. The investigation of a cancer cluster in a steel mill in Ontario attempted to determine if occupational exposures to polycyclic aromatic hydrocarbons and silica were responsible for an increased risk of lung cancer. Even with extensive air monitoring data, no significant findings pertaining to environmental exposures were observed (Finkelstein and Wilk 1990). A more recent cluster investigation of an excess number of cancers within a police detachment in British Columbia involved the follow-up of 174 police personnel who where associated with the detachment since 1963 (van Netten, Brands et al. 2003). Sixteen cases of cancer were identified, however there was no evidence for an underlying event or exposure that could be attributed to the observed cancer cases. The authors discussed the possible role of police radar on the rate of cancer in the detachment.

Health agencies in the US, Canada, and Europe have established protocols for investigating reported cancer clusters. These protocols may differ in some of the specific steps but they do follow a basic procedure in which increasingly more specific information is gathered and analyzed in stages. In the Netherlands, a step wise protocol going from exploratory, qualification, and quantification stages is used (Drijver and Woudenberg 1999). Through each of the three stages, attention is focused both on exposures and disease, and decisions about possible causality are made at the end of each stage. Additionally, as with most cluster protocols, at the end of each stage a decision to

progress with the investigation is made (Fiore, Hanrahan et al. 1990; Aldrich and Sinks 2002).

The primary objective of a cancer cluster investigation is to identify exposures that may be associated with excess cases in a workplace or location so that exposures can be controlled. When conducting a cluster investigation it is useful to consider a number of questions as the work proceeds through the various stages. The initial questions are: (1) is the incidence of disease really higher than normal and by how much? (2) is the exposure higher than normal or the allowable limit? and (3) is the link between exposure and cluster biologically plausible (Quataert, Armstrong et al. 1999)? The stages of a cluster investigation allow for the collection of the necessary information to answer these questions and if these answers are affirmative then the investigation may progress to a full-scale epidemiological study attempting to determine the association between the exposure and increased risk.

Very detailed protocols for investigating reported cancer clusters have been published by health agencies and reviews have appeared in peer-reviewed literature (Kipen and Wartenberg 1988; Caldwell 1990; Fiore, Hanrahan et al. 1990; Frelick and Topham 1991; Smith and Neutra 1993; CCR 1998; Cartwright 1999; WSDOH 2001). In British Columbia, the protocol includes: Stage 1 – Initial contact and response, Stage 2 – Assessment, case evaluation and incidence evaluation, Stage 3 – Major feasibility study, and Stage 4 – Etiologic investigation (CCR 1998). In the State of Washington, their 18 page protocol has similar stages: (1) collect initial information and provide education and information to the informant, (2) assess the magnitude of the reported cluster, (3) determine utility and feasibility of further epidemiologic study, and (4) conduct detailed etiological investigation (WSDOH 2001). Other health departments have developed very similar systematic approaches to cluster investigations and all provide detailed procedures for data collection, analysis, and guidelines for making decisions at the end of each stage (Fiore, Hanrahan et al. 1990).

Analysis of MMHL Cancer Incidence Data: Epidemiology and Statistics

Analysis of records and interviews of present MMHL employees identified 57 employees who were employed in the MMHL for periods exceeding one year over the last 30 years. We were unable to contact 10 individuals and they were excluded from the data analysis. The mean duration of employment at the MMHL for these 10 excluded subjects was 4.6 years. One subject was also excluded because she reported having a diagnosis of cancer before beginning employment at MMHL. Eleven total cancers were reported among the subjects and were of the following types: breast (6), ovarian (1), liver (1), thyroid (1), lymphoma (1) and skin (1). Since the BC Cancer Agency's rates for "all cancers" does not include skin cancer, the subject reporting skin cancer was considered disease free for the statistical analysis. Thus, the observed number of cancer cases in the study group was 10.

A total of 46 employees met the criteria for inclusion in the data analysis. Nine of the 42 women in the study reported a cancer diagnosis whereas 1 of 4 men reported cancer. The

mean age for all 46 employees was 46.4 years and the mean duration of follow-up was 15.3 years. The mean age of individuals reporting cancer (both breast and cancer at other sites) was higher than for those not reporting a diagnosis. The mean age, gender, and duration of follow-up are shown in Table 3.

Table 3. Age, gender and duration of follow-up by disease status

	No Cancer	Breast Cancer	Other Cancer	Total
Females	33	6	3	42
Males	3	0	1	4
Mean Age (yrs)	44.3 (10.1)	54.2 (11.4)	53.8 (10.8)	46.4 (10.9)
Mean duration of follow-up (yrs)	15.9 (7.2)	14.2 (10.5)	12.1 (8.1)	15.3 (7.7)

Data presented as frequency, mean (standard deviation).

A total of 704.01 person-years of observation were available for the data analysis (based on start of employment to end of follow-up for all 46 employees). The distribution of person-years of observation by calendar year is shown in Table 4. Since the majority of employees in the study were women and the fact that breast cancer rates are much higher in women, analyses were conducted in which the four males were excluded. Tables 5 and 6 present the person-years of observation for women in the study, grouped by age and calendar year.

Table 4. Person-years by calendar year for all employees

Calendar year	Person-years	Calendar year	Person-years
1964	0.50	1984	16.79
1965	1.00	1985	18.14
1966	1.00	1986	19.12
1967	1.00	1987	21.76
1968	1.00	1988	22.00
1969	1.00	1989	23.32
1970	1.00	1990	25.61
1971	1.00	1991	30.05
1972	1.17	1992	32.66
1973	2.00	1993	33.99
1974	2.33	1994	35.88
1975	4.35	1995	36.82
1976	5.16	1996	37.02
1977	6.30	1997	37.41
1978	8.00	1998	38.00
1979	8.59	1999	38.00
1980	11.27	2000	37.87
1981	13.06	2001	38.96
1982	14.76	2002	39.00
1983	15.42	2003	21.72
		Total	**704.01**

n = 46 male and female employees

Table 5. Person-years by age group in women in cancer cluster study

Age group (yrs)	Person-years
15 – 19	1.34
20 – 24	41.71
25 – 29	99.54
30 – 34	119.92
35 – 39	105.76
40 – 44	101.23
45 – 49	75.58
50 – 54	50.41
55 – 59	25.16
60 – 64	13.49
65 – 69	5.00
70 – 74	2.58
Total	**641.72**

n = 42 female employees

Table 6. Person-years by calendar year for women in cancer cluster study

Calendar year	Person-years	Calendar year	Person-years
1972	0.17	1988	21.00
1973	1.00	1989	22.32
1974	1.33	1990	24.61
1975	3.35	1991	28.43
1976	4.16	1992	30.66
1977	5.30	1993	31.99
1978	7.00	1994	33.88
1979	7.59	1995	34.82
1980	10.27	1996	34.37
1981	12.06	1997	34.41
1982	13.76	1998	35.00
1983	14.42	1999	35.00
1984	15.00	2000	34.87
1985	16.14	2001	35.96
1986	17.12	2002	36.00
1987	19.76	2003	19.98
		Total	**641.72**

n = 42 female employees

The expected number of cancers, adjusted for age and calendar year, for all 46 employees in the study was 1.51. For females only, the expected number of breast cancers was 0.56 and total cancers was 1.47. These expected cancer cases reflect the number of cases that would have occurred if the cohort of individuals (total employees or female employees) experienced the same rate of cancer as the BC population. The computation of expected numbers of cases is adjusted for both the age of each individual as well as the calendar years that they were at risk. The findings from the statistical analyses are presented in Table 7.

Table 7. Observed and expected cases and age /calendar-year adjusted standard incidence ratios (SIRs) for breast cancer (females only) and all cancers.

	Person-years	Number of subjects	Expected cancers	Observed cancers	Standard Incidence Ratio	95% Confidence Intervals
Breast Cancer	641.72	42	0.56	6	10.7	3.92-23.3
All cancers (females only)	641.72	42	1.47	9	6.1	2.79-11.6
All cancers (all subjects)	704.01	46	1.51	10	6.6	3.17-12.1

The finding of a SIR of 10.7 for breast cancer with 95 percent confidence intervals exceeding 1.0 indicate that the expected number of breast cancers was significantly elevated. The SIR of 10.7 indicates that the women in the MMHL were experiencing breast cancer incidence at approximately ten times the rate than women in the BC population. The 95 percent confidence intervals suggest that, with 95 percent certainty, the increased rate ranged from 3.9 to 23 times higher than the BC rates. Similarly, the standard incidence rates for all cancers in both men and women were significantly elevated as compared to the rates in BC. However, given the large proportion of cancers that were of the breast, the excess in the total cancer SIRs was driven by the high number of reported breast cancers in the employee cohort.

The incidence rate for breast cancer is computed by dividing the person-years of observation for women employees by the number of reported breast cancer cases. This rate was 896 per 100,000 person-years in the study population, and as a comparison, the average incidence rate in BC for breast cancer (all ages) in 2000 was 120 per 100,000 persons.

Field Investigations – Potential Exposures to Potentially Carcinogenic Substances or Physical Agents

The walk-through investigation was conducted in August 2003 and included a review of the current procedures that may result in employee exposures to chemical or physical agents. Questions were asked about past practices and exposures to gain an understanding about how exposures may have changed over the years.

Key points from the walkthrough are provided below:

- Current chemical exposures are minimal because liquid volumes are small and handling is often minimized through the use of "lock and load" systems

- Exposures to physical agents, such as ionizing radiation and electromagnetic fields appears to not be excessive (heat and noise exposures were also minimal)
- Past exposures were likely much higher as a number of procedures have been modified due to technological advances
    - A major change was in the preservation of tissue samples, tissue staining, and glucose measurement. These procedures, in the past, required open use of solvents and reagents which included formalin, xylene, and *o*-toluidine. Most of these procedures were performed in a separate area of the laboratory, which was removed when the procedures were modified. It should be noted that *o*-toluidine, which was discussed in the literature review, is a rat mammary carcinogen, and formaldehyde (the major component in formalin) is a known human carcinogen.
    - Other areas of the laboratory also were renovated due to changes in laboratory procedures. Remnants of a local exhaust ventilation system are present in one area where open chemicals were once mixed and dispensed.
- Poor indoor air quality was a common complaint in the past but appears to be less of a problem currently. An incinerator at the hospital was a source of very odourous and potentially toxic compounds (likely acid gases and possible combustion products of PVC (monomers of vinyl chloride) and other plastics (halogenated organics)).

Previous air quality studies have been performed at MMHL, however investigators did not have access to the findings. In discussions with occupational health and safety professionals at FHA, it was mentioned that all measured concentrations of air contaminants were below regulated limits.

Summary and Recommendations

These findings provide evidence that the female employees within MMHL experienced an elevated rate of breast cancer over the past 30 years. The SIR of 10.2 for breast cancer is statistically significant and the magnitude of the increase rate is of concern. Previous studies have identified nurses and workers in clinical laboratories at higher risk of breast cancer; however, these investigations have not found the magnitude of excess risk found in this study. These previous studies were not designed to determine the causal factors associated with the increased breast cancer risk in laboratory employees or nurses, but it is likely that reproductive factors such as delayed first full-term pregnancy and nulliparity were important in explaining the excess risk.

In our study we did not gather personal information pertaining to known risk factors for breast cancer. The reason for not gathering this information was that this is a preliminary epidemiological study and information on risk factors is difficult to interpret without a comparison population where the prevalence of risk factors is available. For example, in our study if we had detailed information about reproductive factors, family history of breast cancer, socioeconomic factors, alcohol consumption, physical exercise, and obesity, we would only be able to compare the prevalence of those factors with those within the general population. Thus, such data would provide clues as to the possible

reasons for the elevated risk – if the prevalence of these risk factors were the same as the general population it would suggest that occupational factor(s) predominate. Only a full scale, etiologic investigation would have the capability of clearly identifying occupational factors as attributable to the increased breast cancer risk.

A full-scale epidemiologic study may not be the most appropriate action to take despite the increased rates of cancer MMHL employees have experienced. The major goal of cluster investigations is to identify risk factors so that action can be taken to reduce exposures and risk. Air quality studies and reviews of procedures indicate that current exposures to carcinogens are minimal. Past exposures to chemicals like *o*-toluidine may have resulted in some increased risk for employees, but these exposures appear to have been eliminated.

Another issue that discourages a major epidemiologic investigation pertains to the statistics of clusters themselves. Cluster research has shown that elevated rates occur by chance at some geographic locations and times. In fact, clusters always occur and it is a statistical phenomenon – even when there is no causal factor that is responsible for the increased incidence (this is why so few cluster investigations uncover any new risk factors). So, if we look around at many geographic areas and times we will find some clusters; if a specific cluster is related to statistics and not an etiologic agent, it is most likely that in the next time period at this location the rate will not be significantly elevated. Thus, it would be very prudent to continue to evaluate the incidence of breast cancer in MMHL employees to see if the rate comes closer to what is expected.

In summary, this study confirmed that the perceived cluster was an observed cluster and that MMHL employees were experiencing an elevated rate of breast cancer. The factors associated with this increased incidence could not be determined but may have been due to: (1) a cluster of reproductive and other known, nonoccupational, risk factors, (2) past exposures to chemical carcinogens and less likely to ionizing radiation, and (3) a chance occurrence (statistical anomaly).

Our recommendations for action to be considered are: (1) conduct a thorough inventory of all chemicals currently used in the laboratory and identify any that are listed as animal or known/potential human carcinogens (listing from IARC, NTP, etc.). If any listed compounds are used, conduct a detailed exposure assessment; (2) ensure that exposures to ionizing radiation (one of the few known environmental risk factors for breast cancer) are at background; (3) provide education to all employees about risk factors for breast cancer and the importance of self exams and mammography; (4) continue to collect information on the incidence of breast and all cancers in the future so that SIRs can be computed; and (5) if information as to the possible causes of the high SIR is needed, collect information on known risk factors for breast cancer from all employees and send employee information to the BC Cancer Agency for linkage with the cancer registry.

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Attachment 3

An Investigation of a Cancer Cluster within the Mission Memorial Hospital Laboratory March 2004

An Investigation of a Cancer Cluster within the Mission Memorial Hospital Laboratory

March 2004

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ABSTRACT

An excess in the number of cases of cancer was suspected by employees of the Mission Memorial Hospital Laboratory and this investigation was conducted in response to the above concern. The study had three parts, an epidemiologic cluster analysis, a comprehensive review of the literature on breast cancer risk factors and the analysis of clusters, and an exposure investigation. A total of 57 individuals were identified as having worked in the laboratory between January 1, 1970 and August 31, 2003. Information on health status and diagnoses of cancer was obtained through personal interviews with employees. Ten employees reported a cancer diagnosis, of which 6 were breast cancer. A total of 751 person-years of observation were available for the data analysis after excluding one subject because of diagnoses of cancer prior to start of employment. Based on the age and calendar-year adjusted rates for the BC population, the expected number of breast cancer cases in the women was 0.59 and the expected number of all cancers for all employees was 1.60. The Standard Incidence Ratios (SIR), which are the observed number of cases divided by the expected number, were 10.2 for breast cancer in women, and 6.3 for all cancers in both men and women. The 95 percent confidence intervals indicate both findings were significant. A walk-through survey of the laboratory did not identify any potentially hazardous exposures. Recommendations include a comprehensive assessment of all potential exposures to chemicals and physical agents, continuing to collect epidemiological information to determine temporal trends in the SIR, providing information on breast cancer risks to employees, and collecting information on known risk factors for breast cancer and confirming cancer diagnoses through linkage with the BC Cancer Agency's registry.

Introduction

The Occupational Health and Safety Agency for Healthcare (OHSAH) was invited by the Fraser Health Authority (FHA) to investigate concerns of a greater than expected number of cancer cases in the Mission Memorial Hospital Laboratory (MMHL). In addition to the seemingly high total number of cancer cases, a large proportion were the same type (breast cancer) thus further highlighting the need for an investigation. Occupational health professionals from FHA had completed some exploratory work on the project but felt they needed the help of outside experts to resolve the issues. OHSAH conducted a preliminary cluster investigation which is the focus of this report. Dr. Philip Bigelow, a senior scientist at OHSAH, led the investigation and team members included Dr. Annalee Yassi, Rosemary Nemanishen, Dr. Shicheng Yu and William So Yiu Ting. Assistance was also obtained from Dr. Nhu Lee of the British Columbia (BC) Cancer Agency and Dr. Martha Vela Acosta of the Department of Environmental and Radiological Health Sciences at Colorado State University.

Cancer clusters are the occurrences of greater numbers of the same type of cancer, or all cancers, within a geographic location over a specified period of time. The purpose of a cancer cluster investigation is to determine if the observed number of cases is higher than expected. If the observed number is higher, the study should provide information that may help to reduce or eliminate exposures that may be associated with the increased risk. Cancer cluster investigations are often conducted by health agencies and this investigation followed general guidelines recommended by the BC Cancer Agency and public health departments in other jurisdictions across North America (Schulte, Ehrenberg et al. 1987; Caldwell 1990; Cartwright 1999; WSDOH 2001). Prior to the investigation, an explanatory meeting was held at Mission Memorial Hospital to discuss the incidence of cancer at MMHL and the protocol for the investigation. Details of the protocol used during the investigation are provided below.

Methods

The specific aim of this study was to provide a thorough determination if an excess in the number of cancer cases had occurred in the Mission Memorial Hospital Laboratory (MMHL) and to provide information regarding the possibility that a work-related factor was involved. More importantly, the goal was to ensure that current workplace conditions and exposures are not at all likely to result in an increased risk of cancer for employees.

The BC Cancer Agency, as well as other health agencies, have adopted standard protocols for investigating clusters. The methods used in our study followed these standard procedures and included determining if an excess number of cancers was reported, a literature review on the risk factors for the specific cancer types, assessing the potential for occupational exposures to potentially carcinogenic physical agents or substances, and determining the feasibility of further epidemiology studies. Our study was divided into three components as listed below.

1) Analysis of Cancer Incidence Data: Epidemiology and Statistics

Since the concern pertained to employees in the MMHL, only employees who worked in the Laboratory were included in the study. Using data from the Human Resources Department at Mission Memorial Hospital, all employees who were employed in the Laboratory over the past 33 years (January 1970 to August 2003) were identified and this information was provided to an occupational health professional at Fraser Health. A total of 57 individuals were identified and the following information was entered into a computer spreadsheet: date of birth, dates of employment at the lab, job title, full or part time employment status, gender, and other details pertaining to work at the lab and hospital. A health professional (Registered Nurse) from Fraser Health attempted to contact all 57 individuals (in person or by telephone) to gather information on whether or not they had a diagnosis of cancer of any type. For individuals who reported a cancer diagnosis, information on the diagnosis date, type and site of cancer was obtained. Data for all 57 individuals, without personal identifiers, were entered into a spreadsheet and provided to OHSAH.

The statistical analysis was conducted two ways. In one, the person-years of observation was defined as being from the start date of employment at MMHL to the end date of employment. In the second analysis, the person-years of observation was defined as the time between the employee start date and the end of the follow up period (August 2003). In this report the latter analysis is provided, as it is the most appropriate for the study design that was used.[1]

Since a large proportion of the cases were classified as breast cancers, statistical analyses were conducted using rates of breast and total cancers obtained from the BC Cancer Agency. Rates for breast and total cancers for each year from 1970 to 2002, grouped by 5-year age intervals, were used to calculate the expected number of cases in the study group. The expected number of cases is the number of cases expected in the Laboratory if the rate was the same as the rate in BC adjusted for age and calendar year.[2] The expected number of cases was computed by multiplying the population (person-years of observation) within each specific age range and year by the rate of breast or total cancers for the same age interval and year. The results of these computations were summed across all the age and year categories to get the total number of expected cases. Computations and statistical analyses were conducted using Excel and SPSS software.

[1] In many occupational cohort studies, when subjects leave employment their health status at that time is known and their end date of employment is used in the computation of person-years of observation. In this study, we contacted all study subjects from August to November, 2003 to determine their health status.

[2] The risk of developing breast cancer was different in 1980 as compared to today. Additionally, age is a major risk factor for all cancers (including breast cancer). Therefore, crude incidence rates may be misleading when comparing regions or time periods where the age of the populations differ from one region to another or from one time period to another. In this study, the expected number of breast and total cancers was adjusted for age and calendar year and this provides the most accurate comparison of rates for this study.

The observed number of cases was divided by the expected number of breast cancer and total cancer cases to determine the Standard Incidence Ratios (SIR). A SIR exceeding 1.0 indicates the observed number is higher than expected. Confidence intervals are used to assess variation in the SIR and 95% Poisson confidence intervals were calculated using the procedure suggested by Breslow (Breslow 1987). To investigate the relationship of occupational factors on the rate of developing breast cancer, a Cox proportional hazard model was developed that included independent variables for job title, job status (full or part time) and age at start of employment at the laboratory.

2) Field Investigations: Possible Exposures to Potentially Carcinogenic Substances or Physical Agents

Prior to this investigation, work had been conducted by occupational health professionals at Fraser Health to determine the adequacy of procedures to control exposures to chemicals in the laboratory and to ensure exposures did not exceed government or consensus standards. Investigations also focused on potential sources of chemical exposures resulting from work tasks that are typically performed by laboratory personnel. An additional study included Additionally, studies that involved reviewing past renovations of the laboratory in hopes of identifying unusual sources of indoor air contaminants were performed.

In August of 2003, as part of OHSAH's investigation, a walk-through survey of the laboratory was completed. Typical work procedures were reviewed to assess the potential for exposures to hazardous agents. Employees in the laboratory provided information on historical procedures as well as an indication of the general levels of exposure to air contaminants.

3) Literature Review

The investigation and response to cancer cluster reports is exceedingly complex and the report includes brief literature reviews on risk factors for breast cancer, exposures in laboratories, and epidemiology of cancer clusters. This information is provided to help interpret the study findings and provide guidance in deciding whether further study is warranted.

Results and Discussion

The literature review is presented first as it provides a background for interpreting the findings from both the epidemiologic analysis and the field surveys. The literature review of breast cancer highlights the multifactorial nature of disease causation and the difficulties in determining the role of environmental and occupational exposures as causal factors. There is a substantial body of literature on cancer cluster investigations and a brief review is provided. Finally, the findings of the statistical analysis are provided and discussed in relation to findings from other studies.

Literature Review: Breast Cancer Risk Factors and the Role of Occupational and Environmental Exposures

Breast cancer. Canada has one of the highest rates of breast cancer incidence and the age standardized rate in 1995 exceeded 225 per 100,000 women aged 40 and over (Jacobzone 2002). Breast cancer is the most frequently diagnosed cancer in Canadian women and it accounts for over 30% of new cancer cases per year (NCIC 1999). It is estimated that one in nine women in Canada will develop the disease in their lifetime (DeBruin and Josephy 2002). Breast cancer mortality increased steadily from the 1960s until the early 1980s when the rates declined in most countries including Canada (Parkin, Bray et al. 2001; Parkin, Bray et al. 2001). These declining mortality rates are thought to be related to improved screening resulting in earlier detection and improved treatment.

Age is major risk factor for breast cancer and Table 1 shows the increased likelihood of a woman developing breast cancer in the next five years at various ages (PPHB 2004). In addition to age, many correlates of risk for breast cancer have been identified and there are a constellation of hormone-related reproductive factors that predominate. Factors known to confer higher risk include younger age at menarche, older age at menopause, nulliparous, and older at first live birth (Davis, Axelrod et al. 1997). Higher parity, longer lactation, and bilateral ovariectomy have been found to be protective (Davis, Axelrod et al. 1997; Kreiger, Sloan et al. 1999). Using data from large population-based surveys in the United States (US), investigators calculated that 41% of breast cancer risk was explained by nulliparity, later childbearing, higher income, and family history of breast cancer (Madigan, Ziegler et al. 1995). Other risk factors for breast cancer include a history of certain types of benign breast disease as well as high levels of radiation exposure to the chest (medical x-rays) (PPHB 2004). Despite the many studies that have been conducted, additional factors, likely modest in magnitude, remain to be discovered. Interestingly, in 76% of women who develop breast cancer, age is the only identifiable risk factor (Halls 2003).

Table 1.[3] Probability of developing breast cancer in the next five years.

Age	Breast cancer per 1,000 women
30	1.5
35	2.6
40	4.8
45	7.8
50	9.2
55	10.6
60	12.9
65	14.3
70	15.4
80	15.5

Epidemiological and animal studies consistently show elevated risk of breast cancer with factors that increase exposure to estradiol, progesterone, and other hormones (Kreiger, Sloan et al. 1999; Medina 2004; Recchia, Vivacqua et al. 2004; Zeleniuch-Jacquotte, Shore et al. 2004). Risk factors such as alcohol consumption, weight gain after menopause, low pre-menopausal body mass index, and lack of physical exercise are believed to be associated with exposure to reproductive hormones (Hamajima, Hirose et al. 2002; McTiernan, Rajan et al. 2003; Patel, Press et al. 2003; Yang, Bernstein et al. 2003). Pharmaceutical hormones appear to have a similar effect and there is evidence that women exposed to diethylstilbestrol during pregnancy had increased risks for breast cancer (Laitman 2002; Schulmeister 2003). For oral contraceptives, recent use, not long term exposure, has been associated with an increased risk (Burkman 1999; Deligeoroglou, Michailidis et al. 2003). Similarly, recent use of hormone replacement therapy has been shown to increase the relative risk of breast cancer, whereas women who stopped over 5 years ago are not at significantly elevated risk (Vassilopoulou-Sellin 2003).

In epidemiological studies higher socioeconomic status, as measured by income and education level, are consistently associated with elevated breast cancer risk (Mackillop, Zhang-Salomons et al. 2000; Gordon 2003). Although some of this association may be due to a clustering of reproductive risk factors in higher socioeconomic status women, the effect is still significant even after controlling for parity, age at first child and other common reproductive factors (Brody and Rudel 2003). Diet has been well studied but epidemiological investigations have yet to identify foods that significantly increase or decrease breast cancer risk (Higginbotham, Zhang et al. 2004). It is hypothesized that

[3] From PPHB (2004). Breast Cancer in Canada. online at: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/updates/breast-99_e.html, Population and Public Health Branch, Health Canada, Ottawa, Canada. **2004**.

dietary factors may modulate hormone levels so a number of investigations have focused on foods high in phytoestrogens (Hargreaves, Potten et al. 1999; Sarkar and Li 2003) (partial estrogen agonists) or containing other endocrine active components (Brody and Rudel 2003).

Studies of occupational and environmental factors. Animal studies have provided important information in understanding mechanisms of the development of breast cancer and in the identification of agents that may increase breast cancer risk. A comprehensive review of chemical carcinogenesis in general is beyond the scope of this paper, but it should be noted that all cancer causing agents, physical or chemical, will also have the potential to initiate or promote breast cancer. A good example is ionizing radiation which is know to cause cancer at multiple sites; based on human epidemiological studies, it is one of the few occupational or environmental exposures that is a known cause of breast cancer (Land, Tokunaga et al. 2003; Ron 2003).

Studies indicate that estrogen receptor (ER) alpha mediates the breast cancer promoting effects of estrogen. Estradiol binds to ER alpha and induces estrogen receptor-mediated transcription, DNA synthesis, cell division, and cell proliferation which is associated with an increase in errors in DNA transcription. Estrogen and progesterone, both essential for mammary gland growth and function, cause cell proliferation and may be procarcinogenic (DeBruin and Josephy 2002). Both estrogen and progesterone are cytotoxic as they interact with specific receptor proteins in the cell nucleus. Recent research provides evidence that estrogens can be metabolically activated to genotoxic compounds that induce oncogenic mutations (Yue, Santen et al. 2003). Thus, the carcinogenicity of estrogens, as well as their action in increasing susceptibility, may be related to a receptor mediated stimulation of cellular proliferation. Human studies have provided some evidence to support this hypothesis (Wang, Allen et al. 2000). Even without a complete understanding of the mechanism, it is clear that lifetime exposure to estrogen and other hormones explains many identified risk factors for breast cancer.

Cells within the breast are not fully differentiated until they are induced by hormonal stimuli at the woman's first pregnancy and lactation. Thus, breast cells are more susceptible to the effects of carcinogens while the breast is not fully developed. Additionally, the breast cells are vulnerable to genotoxic agents during pregnancy as there is rapid proliferation of cells (Russo and Russo 1996; Russo and Russo 1997). This explanation of the susceptibility of mammary cells to carcinogens provides a framework for understanding the increased risk of breast cancer in humans in relation to reproductive events as well as after exposure to mammary carcinogens. It has been hypothesized that, because the breast is very susceptible to carcinogen exposures up until the first full-term pregnancy, there may be an interaction of age (a known risk factor) and the risk associated with exposures to chemicals (Brody and Rudel 2003).

Despite the complex mechanisms and interactions between chemical exposures and hormones, animal studies have clearly identified numerous mammary carcinogens through standard cancer bioassays. The US National Toxicology Program (NTP) has tested over 500 chemicals and identified 42 as causing mammary tumors (Bennett and

Davis 2002). The human evidence for identifying chemicals causing breast cancer is more scant and of the 42 chemicals cited above, only four are classified as human carcinogens: benzene, 1,3-butadiene, ethylene oxide, and C I acid red 114. Also, it should be noted that epidemiology studies of these compounds have shown exposed employees at higher risk of cancer, but not specifically breast cancer. Mammary carcinogens that may be associated with exposures in chemical and medical laboratories are presented in Table 2 below.

Table 2.[4] Chemicals tested by NTP that produce mammary tumors in experimental animals

Chemical	Use
Acronycine	Pharmaceuticals
Benzene	Gasoline, solvent
2,2-bis(bromomethyl)- 1,3-propanediol	Flame retardant
1,3-Butadiene	Auto exhaust, rubber manufacture, gasoline
C,1 acid red 114	Dye for silk, jute, wool, leather
C,1 basic red 9 monohydrochloride	Dye for textiles, leather, paper, biological stain
2-Chloroacetophenone	Flame retardant
Chloroprene	Used in neoprene manufacture
Clonitralid	Molluskicide
Cytembene	Pharmaceuticals
2,4-Diaminotoluene	Intermediate in dye synthesis
1,2-Dibromo-3-chloropropane	Soil fumigant, pesticide
1,2-Dibromoethane	Soil fumigant, lead scavenger in gasoline
1,2-Dibromo-1-propanol	Flame retardant
1,1-Dichloroethane	Solvent
1,2-Dichloroethane	Solvent, chemical intermediate in insecticide formulations, gasoline
1,2-Dichloropropane (propylene dichloride)	Chemical intermediate, solvent in dry cleaning fluids, fumigant
Dichlorvos	Pesticide
1,2-Dimethoxybenzidine dihydrochloride	Dye intermediate
3,3-Dimethylbenzidine dihydrochloride	Dye intermediate
2,4-Dinitrotoluene	Dye intermediate, explosives, propellants
Ethylene oxide	Sterilizing gas for medical equipment
Furosemide	Pharmaceuticals
Glycidol	Stabilizer in vinyl polymers, intermediate in pesticides and fragrances
Hydrazobenzene	Dye intermediate, tobacco pesticides, motor oil
Isophosphamide	Pharmaceuticals
Indium phosphide	Microelectronics, semiconductors, injection lasers, diodes
Isoprene	By-product of ethylene production
Methylene chloride	Solvent, furniture stripper, adhesives
Methyleugenol	Food additive, flavoring, also naturally occurring
Nithiazide	Antiprotozoal compound
5-Nitroacenaphthene	Research chemical
Nitrofurazone	Antibiotic
Nitromethane	Rocket and engine fuel, solvent, mining explosive
Ochratoxin A	Mycotoxin
Phenesterin	Pharmaceuticals
Procarbazine hydrochloride	Pharmaceuticals
Reserpine	Pharmaceuticals
Sulfallate	Herbicide
2,4- and 2,6-Toluene diisocyanate	Used in manufacture of flexible polyurethane foams
o-Toluidine hydrochloride	Dye intermediate
1,2,3-Trichloropropane	Chemical intermediate, former solvent and paint remover

[4] From Bennett, L. M. and B. J. Davis (2002). "Identification of mammary carcinogens in rodent bioassays." Environ Mol Mutagen **39**(2-3): 150-7.

Both animal and human studies show that the relationships between hormonal factors and mammary carcinogens is complex. Treatment of animals with ovarian, placental, pituitary, and thyroid hormones modulates the tumorgenic responses (Russo and Russo 1998). The situation is further complicated with exposures to chemicals that are members of a class of hormonally active chemicals, sometimes referred to as endocrine active, endocrine disruptors, or estrogenic compounds. The hypothesis is that exposure increases estrogen-like responses of cell proliferation that increase cancer risk. There is also a concern that these endocrine active compounds can act in an additive manner to produce effects (Charles, Gennings et al. 2002; Brody and Rudel 2003).

Chemicals, including some pesticides, also can act as co-carcinogens or tumor promoters (Bounias 2003). A good example of a breast cancer promoter in experimental animals is dichlorodiphenyltrichloroethane (DDT). Experimental animals fed a known mammary carcinogen, and then given DDT, developed breast tumors earlier than when the carcinogen was given alone; however, when DDT was given alone, it did not induce breast tumors in these animals (Snedeker 1997). The human evidence of DDT's effects as a promoter is more equivocal, although a recent study reported significantly elevated mean levels of serum DDT and hexachlorobenzene (HCB) in breast cancer patients as compared to controls (Charlier, Albert et al. 2003). Other organochlorine compounds have been implicated as being associated with an increased risk of breast cancer. The hypothesis is that this group of compounds possess estrogenic activity. However, both the hypothesis and the magnitude of any possible effect on human risk of breast cancer is controversial. Recent reviews suggest that the estrogenic contribution of organochlorine compounds is small in view of the presence of natural hormone and antihormone mimics in our diet (Safe and Zacharewski 1997; DeBruin and Josephy 2002). Other endocrine active compounds, such as alkyl phenols and phthalates are still under investigation (Sonnenschein and Soto 1998).

Studies of breast cancer risk in working populations have not provided strong evidence of causal links between specific exposures and increased risk. However, there is evidence for positive associations of several occupations with increase breast cancer risk (Morton 1995; Goldberg and Labreche 1996; Band, Le et al. 2000). The study by Band et al. (2000) was conducted in British Columbia and found significantly higher breast cancer risks (1) among *pre-menopausal* women in electronic data-processing operators; barbers and hairdressers; in sales and material processing occupations; and in the food, clothing, chemical and transportation industries; (2) among *post-menopausal* women in school teaching; in medicine, health, and nursing occupations; in laundry and dry-cleaning occupations; and in the aircraft and automotive, including gasoline service station, industries. Several significant associations were also seen in the combined group of pre- and post-menopausal women, particularly in crop farmers and in fruit and vegetable farming, publishing and printing, and motor vehicle repair industries. The authors suggested that there was excess breast cancer risk in a number of occupations and industries, notably those that entail exposure to solvents and pesticides (Band, Le et al. 2000).

Shiftwork causes employees to have exposure to light at night and may increase the risk of cancer by suppressing the normal nocturnal production of melatonin by the pineal gland. Melatonin, is not only a hormone that has antiproliferative effects which protect against the development of cancer (Schernhammer, Laden et al. 2003), but it also modulates estrogen release from the ovaries. When nocturnal melatonin production is suppressed, the direct antiproliferative effects are reduced and estrogen release may be increased (Davis, Mirick et al. 2001). In a study of female nurses in a large prospective health investigation, women working a rotating night shift at least three nights per month for 15 or more years were at an increased the risk of colorectal cancer (Schernhammer, Laden et al. 2003). A recent population-based, case-control study found that graveyard shiftwork was associated with increased breast cancer risk (OR = 1.6; 95% CI = 1.0 to 2.5), with a trend of increased risk with increasing years and with more hours per week of graveyard shiftwork (Davis, Mirick et al. 2001).

Clinical laboratory workers have the potential for exposure to a variety of chemical, biological, as well as physical agents (Weaver 1997; Tompa, Major et al. 1999; Bigelow 2000). Despite the fact that chemical and clinical laboratories employ many women (over 1 million in the US), few studies have examined the possible adverse effects of exposures. Burnett et al. (1999) conducted a study to determine if laboratory workers in the US experienced higher cancer mortality rates than those in other occupations. They found clinical laboratory workers had higher proportionate cancer mortality ratios overall (for all cancers) as well as for breast cancer. The proportionate mortality ratios for leukemia were also significantly elevated for clinical laboratory workers (Burnett, Robinson et al. 1999). The authors suggest that the elevated risks for lymphatic and hematopoietic neoplasms may have been associated with occupational exposures.

With the exception of a few studies that have identified very high occupational exposures to carcinogenic compounds as causal factors in breast cancer, most investigations have not been able to clearly determine occupational risk factors (Goldberg and Labreche 1996). The reasons for the failure to identify specific chemicals or physical agents include not only the complex nature of the initiation, promotion, and development of breast cancer, but also the presence of many potential confounding risk factors. Additionally, there appear to be numerous, but so far unidentified, risk factors that the issue of confounding becomes even more salient. Little is known about the interaction of known risk factors on the magnitude of increase in breast cancer risk and even less is known about the possible synergistic, additive, or antagonistic effects of multiple chemical exposures.

The strength of already known breast cancer risk factors makes the identification of occupational risk factors very difficult. When examining the role of these major risk factors, it has been estimated that 41 percent of breast cancer risk is attributable to later childbearing, nulliparity, higher income, and family history of breast cancer (Madigan, Ziegler et al. 1995). Studies that have focused on genetic variation have estimated that less that 10 percent of cases are due to gene mutations in the breast cancer genes *BRCA1* and *BRCA2* (Claus, Schildkraut et al. 1996). Diet, alcohol consumption, physical activity, body mass index, other reproductive factors, high chest radiation exposure, and

exposure to pharmaceutical hormones all account for some risk in the development of breast cancer. In occupational studies, if the likelihood of exposure to these known breast cancer risk factors is increased in an occupational group, an association between the occupation and increased breast cancer risk will be observed. Additionally, the presence of powerful risk factors may mask the effect of an exposure that is truly increasing breast cancer risk.

Traditional epidemiological methods are typically not able to identify occupational risk factors for breast cancer at the levels of exposure seen in modern industry in Canada or the US. Newer methods that include the use of biological markers of exposure and incorporating gene-environment interactions have shown promise. These methods are better able to uncover subtle differences in risk and also provide an understanding of the underlying mechanisms. An example of these cutting edge techniques is the measurement of the aromatic amine, *o*-toluidine, a rat mammary carcinogen, in human milk samples from mothers. The presence of this chemical indicates that the ductal epithelial cells of the breast are exposed to this carcinogen (DeBruin, Pawliszyn et al. 1999). The use of biomarkers and gene-environment interactions have elucidated the complex associations of smoking, polymorphisms of drug metabolizing enzymes, and reproductive factors in breast cancer risk (DeBruin and Josephy 2002). These techniques have not been rigorously applied in studies involving occupational exposures and breast cancer but their use has been advocated (DeBruin and Josephy 2002; Ward, Schulte et al. 2003).

Literature Review: Cancer Clusters

Incidence rates of breast cancer, and all cancers, vary over time and geography and a cancer cluster is generally defined as the occurrence of a greater than expected number of cases of a particular cancer within a group of people, a geographic area, or a period of time. Studying and describing these spatial and temporal trends have provided clues for identifying previously undiscovered causes of cancer. In fact, the first causal relationship between an occupational exposure and cancer was uncovered as the result of a cluster investigation of scrotal skin cancer among young chimney sweeps in London (Pott 1996). Epidemiologists, the scientists most often leading the investigation of clusters, generally encounter clusters because of reports or through discovery from organized analyses of large databases (Kheifets 1993). Although the methods of analysis differ slightly depending on how the cluster is first identified, in both cases the results are difficult to interpret and drawing definitive conclusions is often not possible.

As was discussed in the section on breast cancer risk factors, some variation in breast cancer risk can be explained by the population distribution of known risk factors such as parity, age at first child and other reproductive factors (Robbins, Brescianini et al. 1997). In fact, grouping of reproductive risk factors and socioeconomic status play a major role in the findings of positive associations between white collar occupations and increased risk of breast cancer (Brody and Rudel 2003). However, regional patterns of increased and decreased breast cancer risk may reflect a complex aggregation of diverse factors which may include diet, demographics, lifestyle factors, and occupational and

environmental exposures. Gaining an understanding of these individual factors and their relationships is necessary to have a complete understanding of breast cancer risk in individuals and specific groups of women.

For breast cancer, clusters of relatively high incidence rates have been reported in areas of southern Alberta and British Columbia (NRC 2004). This type of variation by region is common and it is most often unclear whether or not the determinants of these differences are related to environmental, lifestyle, or other exposures. Even in populations that are well studied, such as in the Long Island, New York Breast Cancer Study Project (Wittenberg 1994; Gammon, Neugut et al. 2002), limitations in study design make the finding of significant environmental risk factors unlikely. In most investigations, biological data relating to occupational or environmental exposures is sparse or inadequate and other risk factors are not well controlled. Thus, even very extensive investigations of breast cancer clusters have high probabilities of failing to identify occupational or environmental risk factors (Timander and McLafferty 1998).

Breast cancer cluster investigations are often limited because of the effect of the very strong risk factors related to endogenous hormones that increase breast cancer risk. The question still remains: do exposures to hormone-mimicking chemicals or other chemical and physical agents also exert an effect? A multidisciplinary workshop, titled "Hormones, Hormone Metabolism, Environment, and Breast Cancer," convened by the National Action Plan on Breast Cancer, the US National Cancer Institute, Tulane University, and the U.S. Public Health Service's Office of Women's Health, in September 1995 discussed the complexity of factors, unresolved controversial issues, and the need for improved methodology to measure hormones and their metabolites (NCI 1997). As is the case with occupational studies of breast cancer, molecular as well as bioinformatic techniques were discussed as useful tools in gaining an understanding of the complex relationships between genes, individual factors, and the environment.

Investigating cancer clusters: Methods and limitations

The first of the modern cancer cluster reports began in the 1960s and the increasing number of reports spurred the development of investigation protocols. At a US National Cancer Institute conference on clusters, Dr. Langmuir advocated a simple approach: "The constructive approach to this situation, in my opinion, is not to develop highly refined statistical techniques to determine whether or not a certain cluster may have resulted by chance alone. But, rather to investigate each cluster as it is reported and see if additional associations of possible interest can be found. If none turn up, this is obviously a cold trail, and any good hunting dog will abandon it, and look for a better one. If the scent strengthens, then hot pursuit is in order" (Langmuir 1965).

Langmuir's advice for a simple approach did not deter the development of statistical models to resolve the issue of whether cancer cases were occurring independently or if they appeared to be related. A number of theoretical statistical methods have been developed and modified to detect clusters and to assess the statistical associations of interest. A detailed review of the theories underlying these sophisticated statistical

approaches is beyond the scope of this discussion and interested readers should consult articles describing specific statistical techniques as well as comprehensive reviews of the subject (Langmuir 1965; Schulte, Ehrenberg et al. 1987; Hanrahan, Mirkin et al. 1990; Hall, Lee et al. 1996; Kulldorff, Athas et al. 1998; Knorr-Held and Rasser 2000; Lawson 2000; Gangnon and Clayton 2001). Most of the models developed are useful when information is available on the observed cases in many discrete geographic locations and time intervals; the models then provide the likelihood of any one discrete location/time interval having a number of cases that is excessive. Thus, these techniques have most utility when there is routine monitoring of cases across large geographic areas (i.e., province-wide or Canada-wide surveillance programs).

The detection and analysis of cancer clusters most often is the responsibility of public health agencies such as local health departments, state or provincial health authorities, cancer registries, or national health agencies (Health Canada or the US Centers for Disease Control (CDC)). The Canadian Cancer Incidence Atlas is a recently developed national atlas that assesses the significance and spatial correlation of the age-standardized rates for 290 census divisions across the country (Semenciw, Le et al. 2000). The Atlas provides information about cancer incidence rates and is able to determine if cancer rates are significantly elevated in certain areas. As discussed previously, the Lower Mainland of BC is one area in which breast cancer incidence rates are significantly elevated as compared to the national average (NRC 2004).

When a cancer cluster is first reported, usually by concerned employees or citizens, the cluster is termed a *perceived cancer cluster*. If an investigation determines that the observed number of cases significantly exceeds the expected number it is termed an *observed cancer cluster*. If, after further investigation, a risk factor can be identified the cluster is called an *etiologic cancer cluster* (Aldrich and Sinks 2002). In investigating cancer clusters the goal is to determine if the cluster is real (observed cancer cluster); and, if it is real, to determine if it is or is not an etiologic cancer cluster. If the investigation uncovers an etiologic cancer cluster, efforts should be made to reduce/modify the causal factors (exposures) that are responsible for the increased risk.

Public concern pertaining to environmental exposures and cancer resulted in the reporting of many perceived cancer clusters over the past 20 years (Trumbo 2000; Siegrist, Cvetkovich et al. 2001). Public health authorities responded to these concerns by conducting investigations that varied in scope and cost. Considerable resources were allocated to cluster investigations and most did not identify etiologic cancer clusters. The US CDC, from 1961 to 1982 investigated 108 reported cancer clusters in 29 states and 5 foreign countries; no clear cause of cancer was determined for any of the reported clusters (Caldwell 1990). The Minnesota Department of Health (MDOH) investigated more than one thousand cancer clusters between 1984 and 1995 without identifying a particular cause in any (Garry, Jacobs et al. 1989). As a result of these many investigations, the MDOH developed a widely adopted systematic approach for cluster investigations (Bender 1987; Bender, Williams et al. 1990).

Cancer clusters also occur in the workplace and a number of the classic exposure-disease relationships arose from investigations of clusters. The determinations that polycyclic aromatic hydrocarbons, asbestos, and vinyl chloride monomer are human carcinogens were made though analyses of cancer clusters in workers where these products were manufactured or used (Lieben 1966; Lieben and Pistawka 1967; Pott 1996; Lewis and Rempala 2003). These etiologic clusters occurred before modern industrial hygiene controls were implemented and resulted from very high exposures to potent carcinogens. These early occupational cancer cluster investigations were effective in identifying and controlling large cancer risks that workers faced before the 1970s. Consequently, the role of occupational carcinogens in current clusters is more subtle than in the past and more difficult to detect.

In the US, the National Institute for Occupational Safety and Health (NIOSH), through its Health Hazards Evaluation Branch, is often called upon to investigate reported cancer clusters. In a review of 61 cancer clusters investigations that NIOSH completed between 1978 and 1984, a numerical excess of cases compared with expected numbers was found in 16 of the reported clusters (Schulte, Ehrenberg et al. 1987). In most of the reported clusters, no identified environmental exposure could be identified. In five of the 16 clusters there were exposures to potential carcinogens and the exposure-disease relationship was plausible (sufficient induction time and timing of exposure). Almost all of the investigations were limited by small numbers of cases, absence of complete personnel records, and other methodological and statistical issues that prevented the identification of specific causal occupational risk factors (Schulte, Ehrenberg et al. 1987).

In Canada there have been few published cancer cluster investigations that have identified a specific cause that was occupationally related. The investigation of a cancer cluster in a steel mill in Ontario attempted to determine if occupational exposures to polycyclic aromatic hydrocarbons and silica were responsible for an increased risk of lung cancer. Even with extensive air monitoring data, no significant findings pertaining to environmental exposures were observed (Finkelstein and Wilk 1990). A more recent cluster investigation of an excess number of cancers within a police detachment in British Columbia involved the follow-up of 174 police personnel who where associated with the detachment since 1963 (van Netten, Brands et al. 2003). Sixteen cases of cancer were identified, however there was no evidence for an underlying event or exposure that could be attributed to the observed cancer cases. The authors discussed the possible role of police radar on the rate of cancer in the detachment.

Health agencies in the US, Canada, and Europe have established protocols for investigating reported cancer clusters. These protocols may differ in some of the specific steps but they do follow a basic procedure in which increasingly more specific information is gathered and analyzed in stages. In the Netherlands, a step wise protocol going from exploratory, qualification, and quantification stages is used (Drijver and Woudenberg 1999). Through each of the three stages, attention is focused both on exposures and disease, and decisions about possible causality are made at the end of each stage. Additionally, as with most cluster protocols, at the end of each stage a decision to

progress with the investigation is made (Fiore, Hanrahan et al. 1990; Aldrich and Sinks 2002).

The primary objective of a cancer cluster investigation is to identify exposures that may be associated with excess cases in a workplace or location so that exposures can be controlled. When conducting a cluster investigation it is useful to consider a number of questions as the work proceeds through the various stages. The initial questions are: (1) is the incidence of disease really higher than normal and by how much? (2) is the exposure higher than normal or above allowable limits? and (3) is the link between exposure and cluster biologically plausible (Quataert, Armstrong et al. 1999)? The stages of a cluster investigation allow for the collection of the necessary information to answer these questions and if these answers are affirmative then the investigation may progress to a full-scale epidemiological study attempting to determine the association between the exposure and increased risk.

Very detailed protocols for investigating reported cancer clusters have been published by health agencies and reviews have appeared in the peer reviewed literature (Kipen and Wartenberg 1988; Caldwell 1990; Fiore, Hanrahan et al. 1990; Frelick and Topham 1991; Smith and Neutra 1993; CCR 1998; Cartwright 1999; WSDOH 2001). In British Columbia, the protocol includes: Stage 1 – Initial contact and response, Stage 2 – Assessment, case evaluation and incidence evaluation, Stage 3 – Major feasibility study, and Stage 4 – Etiologic investigation (CCR 1998). In the State of Washington, their 18 page protocol has similar stages: (1) collect initial information and provide education and information to the informant, (2) assess the magnitude of the reported cluster, (3) determine utility and feasibility of further epidemiologic study, and (4) conduct detailed etiological investigation (WSDOH 2001). Other health departments have developed very similar systematic approaches to cluster investigations and all provide detailed procedures for data collection, analysis, and guidelines for making decisions at the end of each stage (Fiore, Hanrahan et al. 1990).

Analysis of MMHL Cancer Incidence Data: Epidemiology and Statistics

Analysis of records and interviews of present MMHL employees identified 57 employees who were employed in the MMHL for periods exceeding one year over the last 30 years. We were unable to contact 10 individuals at the end of the follow-up period (August 2003) and for those individuals their disease status at the time they left employment at the laboratory was determined and used in the analysis. One subject was excluded because she reported having a diagnosis of cancer before beginning employment at MMHL. Eleven total cancers were reported among the subjects and were of the following types: breast (6), ovarian (1), liver (1), thyroid (1), lymphoma (1) and skin (1). Since the BC Cancer Agency's rates for "all cancers" does not include skin cancer, the subject reporting skin cancer was considered disease free for the statistical analysis. Thus, the observed number of cancer cases in the study group was 10.

A total of 56 employees met the criteria for inclusion in the data analysis. Nine of 50 women in the study reported a cancer diagnosis whereas 1 of 6 men reported cancer. The

mean age for all 56 employees was 43.1 years and the mean duration of follow-up was 13.4 years. The mean age of individuals reporting cancer (both breast and cancer at other sites) was higher than for those not reporting a diagnosis. The mean age, gender, and duration of follow-up are shown in Table 3.

Table 3. Age, gender and duration of follow-up by disease status

	No Cancer	Breast Cancer	Other Cancer	Total
Females	41 (73.21%)	6 (10.71%)	3 (5.36%)	50 (89.29%)
Males	5 (8.93%)	0	1 (1.79%)	6 (10.71%)
Mean age at start work (yrs)	29.07 (8.68)	32.03 (11.29)	33.78 (7.53)	29.72 (8.86)
Mean age at end work or end study (yrs)	42.47 (10.67)	46.2 (13.24)	45.90 (7.99)	43.12 (10.70)
Mean duration of follow-up (yrs)	13.41 (8.34)	14.16 (10.50)	12.13 (8.13)	13.40 (8.41)

Data presented as frequency (percent of total), mean (standard deviation); n=56

A total of 751.27 person-years of observation were available for the data analysis (based on start of employment to end of follow-up for all 56 employees). The distribution of person-years of observation by calendar year is shown in Table 4. Since the majority of employees in the study were women and the fact that breast cancer rates are much higher in women, analyses were conducted in which the males were excluded. Tables 5 and 6 present the person-years of observation for women in the study, grouped by age and calendar year.

Table 4. Person-years and distribution of all-causes cancer by calendar year for all employees

Calendar year	Person-years	Number of incidence cases	Calendar year	Person-years	Number of incidence cases
1964	0.50	0	1984	19.79	1
1965	1.00	0	1985	22.14	0
1966	1.00	0	1986	22.12	0
1967	1.00	0	1987	24.76	0
1968	1.00	0	1988	25.92	1
1969	1.00	0	1989	26.32	0
1970	1.00	0	1990	27.96	0
1971	1.00	0	1991	33.05	1
1972	1.17	0	1992	35.51	0
1973	2.00	0	1993	34.99	1
1974	2.33	0	1994	37.21	0
1975	4.35	0	1995	39.57	0
1976	5.16	0	1996	38.02	1
1977	6.30	0	1997	38.58	1
1978	8.00	0	1998	38.00	0
1979	9.59	0	1999	38.00	0
1980	13.27	0	2000	38.77	1
1981	15.06	0	2001	38.96	0
1982	17.75	0	2002	39.00	0
1983	18.42	0	2003	21.72	3
		Total	**(PYRS and cases)**	**751.27**	**10**

n = 56 male and female employees.

Table 5. Person-years and distribution of breast cancer by age group in women in cancer cluster study

Age group (yrs)	Number of incident cases	Person-years	Number of incident cases
15 – 19	0	1.34	0
20 – 24	0	43.95	0
25 – 29	0	100.37	0
30 – 34	0	120.91	0
35 – 39	0	112.67	1
40 – 44	0	113.25	0
45 – 49	0	83.50	1
50 – 54	0	51.58	2
55 – 59	0	25.16	0
60 – 64	0	13.49	1
65 – 69	0	5.00	0
70 – 74	0	2.58	1
Total (PYRS and cases)		**673.80**	**6**

n = 50 female employees

Table 6. Person-years and distribution of breast cancer by calendar year for women in cancer cluster study

Calendar year	Person-years	Number of incident cases	Calendar year	Person-years	Number of incident cases
1972	0.17	0	1988	22.92	0
1973	1.00	0	1989	23.32	0
1974	1.33	0	1990	25.71	0
1975	3.35	0	1991	30.43	1
1976	4.16	0	1992	32.58	0
1977	5.30	0	1993	32.99	0
1978	7.00	0	1994	35.21	0
1979	8.59	0	1995	37.57	0
1980	11.27	0	1996	35.37	1
1981	13.06	0	1997	35.58	1
1982	15.75	0	1998	35.00	0
1983	16.42	0	1999	35.00	0
1984	17.00	1	2000	35.77	0
1985	19.14	0	2001	35.96	0
1986	19.12	0	2002	36.00	0
1987	21.76	0	2003	19.98	2
		Total	**(PYRS and cases)**	**673.80**	**6**

n = 50 female employees.

The expected number of cancers, adjusted for age and calendar year, for all 56 employees in the study was 1.60. For females only, the expected number of breast cancers was 0.59 and total cancers was 1.55. These expected cancer cases reflect the number of cases that would have occurred if the cohort of individuals (total employees or female employees) experienced the same rate of cancer as the BC population. The computation of expected numbers of cases is adjusted for both the age of each individual as well as the calendar years that they were at risk. The findings from the statistical analyses are presented in Table 7.

Table 7. Observed and expected cases and age/calendar-year adjusted standardized incidence ratios (SIRs) for breast cancer (females only) and all cancers.

	Person-years	Number of subjects	Expected cancers	Observed cancers	Standard Incidence Ratio	95% Confidence Intervals
Breast Cancer	673.80	50	0.59	6	10.2	3.74-22.24
All cancers (females only)	673.80	50	1.55	9	5.8	2.66-11.02
All cancers (all subjects)	751.27	56	1.60	10	6.3	3.02-11.59

The finding of a SIR of 10.2 for breast cancer with 95 percent confidence intervals exceeding 1.0 indicate that the expected number of breast cancers was significantly elevated. The SIR of 10.2 indicates that the women in the MMHL were experiencing breast cancer incidence at approximately ten times the rate than women in the BC population. The 95 percent confidence intervals suggest that, with 95 percent certainty, the increased rate was from 3.7 to 22.2 times higher than the BC rates. Similarly, the standard incidence rates for all cancers in both men and women were significantly elevated as compared to the rates in BC. However, given the large proportion of cancers that were of the breast, the excess in the total cancer SIRs was driven by the high number of reported breast cancers in the employee cohort.

The incidence rate for breast cancer is computed by dividing the person-years of observation for women employees by the number of reported breast cancer cases. This rate was 890 per 100,000 person-years in the study population, and as a comparison, the average incidence rate in BC for breast cancer (all ages) in 2000 was 120 per 100,000 persons.

Cox proportional hazard modeling showed that the variables age at start of work at MMHL, job position, and job status were not related to the hazard rate. The hazard rate is defined as the probability per time unit that a person who has not developed cancer to the beginning of the respective interval will develop cancer in that interval. Findings from the proportional hazard model are presented in Table 8.

Table 8. Hazard ratios and 95% confidence intervals (CIs) of breast cancer in relation to age at start of work at MMHL, position, and job status for women

Variables	Hazard Ratio	95% CI	p-value *
Age at start work (yrs)	1.07	0.97, 1.18	0.173
Position			
Technician	1.00		
Aid, clerk or ECG	0.67	0.08, 6.04	0.723
Job status			
Part time or causal	1.00	0.14, 15.06	0.754
Full time	1.45		

* p-value from Cox proportional hazards model with age at start work as a continuous variable and position and job status as categorical variables.

Field Investigations: Potential Exposures to Potentially Carcinogenic Substances or Physical Agents

The walk-through investigation was conducted in August 2003 and included a review of the current procedures that may result in employee exposures to chemical or physical agents. Questions were asked about past practices and exposures to gain an understanding about how exposures may have changed over the years.

Key points from the walkthrough are provided below:

- Current chemical exposures are minimal because liquid volumes are small and handling is often minimized through the use of "lock and load" systems
- Exposures to physical agents, such as ionizing radiation and electromagnetic fields appears to not be excessive (heat and noise exposures were also minimal)
- Past exposures were likely much higher as a number of procedures have been modified due to technological advances
    - A major change was in the preservation of tissue samples, tissue staining, and glucose measurement. These procedures, in the past, required open use of solvents and reagents which included formalin, xylene, and *o*-toluidine. Most of these procedures were performed in a separate area of the laboratory, which was removed when the procedures were modified. It should be noted that *o*-toluidine, which was discussed in the literature review, is a rat mammary carcinogen, and formaldehyde (the major component in formalin) is a known human carcinogen.
    - Other areas of the laboratory also were renovated due to changes in laboratory procedures. Remnants of a local exhaust ventilation system are present in one area where open chemicals were once mixed and dispensed.
- Poor indoor air quality was a common complaint in the past but appears to be less of a problem currently. An incinerator at the hospital was a source of very odourous and potentially toxic compounds (likely acid gases and possible

combustion products of PVC (monomers of vinyl chloride) and other plastics (halogenated organics)).

Previous air quality studies have been performed at MMHL, however investigators did not have access to the findings. In discussions with occupational health and safety professionals at FHA, it was mentioned that all measured concentrations of air contaminants were below regulated limits.

Summary and Recommendations

These findings provide evidence that the female employees within MMHL experienced an elevated rate of breast cancer over the past 30 years. The SIR of 10.2 for breast cancer is statistically significant and the magnitude of the increase rate is of concern. Previous studies have identified nurses and workers in clinical laboratories at higher risk of breast cancer; however, these investigations have not found the magnitude of excess risk found in this study. These previous studies were not designed to determine the causal factors associated with the increased breast cancer risk in laboratory employees or nurses, but it is likely that reproductive factors such as delayed first full-term pregnancy and nulliparity were important in explaining the excess risk.

In our study we did not gather personal information pertaining to known risk factors for breast cancer. The reason for not gathering this information was that this is a preliminary epidemiological study and information on risk factors is difficult to interpret without a comparison population where the prevalence of risk factors is available. For example, in our study if we had detailed information about reproductive factors, family history of breast cancer, socioeconomic factors, alcohol consumption, physical exercise, and obesity, we would only be able to compare the prevalence of those factors with those within the general population. Thus, such data would provide clues as to the possible reasons for the elevated risk – if the prevalence of these risk factors were the same as the general population it would suggest that occupational factor(s) predominate. Only a full scale, etiologic investigation would have the capability of clearly identifying occupational factors as attributable to the increased breast cancer risk.

A full-scale epidemiologic study may not be the most appropriate action to take despite the increased rates of cancer MMHL employees have experienced. The major goal of cluster investigations is to identify risk factors so that action can be taken to reduce exposures and risk. Air quality studies and reviews of procedures indicate that current exposures to carcinogens are minimal. Past exposures to chemicals like *o*-toluidine may have resulted in some increased risk for employees, but these exposures appear to have been eliminated.

Another issue that discourages a major epidemiologic investigation pertains to the statistics of clusters themselves. Cluster research has shown that elevated rates occur by chance at some geographic locations and times. In fact, clusters always occur and it is a statistical phenomenon – even when there is no causal factor that is responsible for the increased incidence (this is why so few cluster investigations uncover any new risk

factors). So, if we look around at many geographic areas and times we will find some clusters; if a specific cluster is related to statistics and not an etiologic agent, it is most likely that in the next time period at this location the rate will not be significantly elevated. Thus, it would be very prudent to continue to evaluate the incidence of breast cancer in MMHL employees to see if the rate comes closer to what is expected.

In summary, this study confirmed that the perceived cluster was an observed cluster and that MMHL employees were experiencing an elevated rate of breast cancer. The factors associated with this increased incidence could not be determined but may have been due to: (1) a cluster of reproductive and other known, nonoccupational, risk factors, (2) past exposures to chemical carcinogens and less likely to ionizing radiation, and (3) a chance occurrence (statistical anomaly).

Our recommendations for action to be considered are: (1) conduct a thorough inventory of all chemicals currently used in the laboratory and identify any that are listed as animal or known/potential human carcinogens (listing from IARC, NTP, etc.). If any listed compounds are used, conduct a detailed exposure assessment; (2) ensure that exposures to ionizing radiation (one of the few known environmental risk factors for breast cancer) are at background; (3) provide education to all employees about risk factors for breast cancer and the importance of self exams and mammography; (4) continue to collect information on the incidence of breast and all cancers in the future so that SIRs can be computed; and (5) if information as to the possible causes of the high SIR is needed, collect information on known risk factors for breast cancer from all employees and send employee information to the BC Cancer Agency for linkage with the cancer registry.

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Attachment 4

PowerPoint presentation
An Investigation of a Cancer Cluster within the Mission Memorial Hospital Laboratory

An Investigation of a Cancer Cluster within a Hospital Laboratory

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  - Dr. Paul Demers (School of Occupational and Environmental Hygiene, UBC)

Introduction

- Report of seemingly high number of cancer cases in laboratory workers
- Need for an epidemiological study
- Purpose of investigation:
  - To determine if cluster had occurred
  - To identify possible occupational factors if a true cluster is identified
  - To ensure current exposures/occupational factors are below recommended standards and current exposures are not increasing the risk of cancer in MMHL employees

Methods - Epidemiology

- Enumeration of the occupational cohort
  - Employee data files for all individuals working from 1970 to 2003
  - Methods for confidentiality
- Analysis of cancer incidence data
  - Collection of data on health status and cancer incidence from personal interviews
  - Data entered into excel and SPSS
  - Rates of cancer and breast cancer from 1970 to 2002 for males and females obtained
  - Person years of observation (PYRS) were computed for study cohort for each age interval (5 yr increments) and calendar year
  - Expected number of cases (breast and all cancers) computed for each age and calendar year category

Breast Cancer Rates and Computation of Expected Number of Cases

FBreastx100,00 0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
1970	0	0	0	0	1.153722	9.534447	22.47155	47.04696	98.0408	171.1503	164.6675	184.5657	252.3378	190.68
person yrs				0	0	0	1	0	0	0	0	0	0	0
1971	0	0	0	0	0	9.872277	27.11824	39.29637	113.3425	205.6203	248.218	219.1901	254.3176	251.95
person yrs				0	0	0	1	0	0	0	0	0	0	0
1972	0	0	0	0.9374	1.005227	7.84947	12.83239	49.61032	98.31436	161.8765	202.9954	248.5001	241.8511	275.71
person yrs					0.083333	0	1	0	0	0	0	0	0	0
1973	0	0	0	0	0.964376	7.341451	17.30795	51.59797	118.5074	176.5951	204.7583	251.2563	273.3532	235.12
person yrs					1	0	1	1	0	0	0	0	0	0
1974	0	0	0	0	1.813615	7.889235	32.11581	39.09774	121.9926	154.3537	209.1224	202.3736	304.1898	255.68
person yrs					1	0	1	1	0.25	0	0	0	0	0
1975	0	0	0	0	0	2.795014	19.79161	62.4102	88.90388	166.5556	203.5073	268.7858	304.6307	256.99
person yrs					1.583333	0	0	1	0.666667	1	0	0	0	0
1976	0	0	0	0	0.843768	4.469673	20.14054	58.77332	115.0148	153.1928	174.5427	273.2811	267.4778	313.33
person years					0.083333	2	0	1	1	1	0	0	0	0
1977	0	1.044976	0	0	0	7.934969	39.48708	38.77472	97.06382	181.1815	215.1104	192.2752	235.8974	242.1
person yrs					1.25	2	0	1	0	2	0	0	0	0
1978	0	0	0	0	0.814545	6.897384	20.5842	64.28923	92.80048	162.9328	183.6711	215.0696	260.0736	312.36
person yrs					2.916667	2	0	0	1	2	0	0	0	0
1979	0	0	0	0	2.383999	10.05151	26.07562	51.17281	95.82438	162.0991	209.9683	221.4242	239.0984	325.16
person yrs					2	3	0	0	1	2	0	0	0	0
1980	0	0	0	0	0.763674	7.224274	17.37363	59.63029	105.4896	180.2289	161.0377	258.5894	261.0714	334.20
person yrs		1		0	1.5	4	0.666667	0	1	1	0	0	0	0
1981	0	0	0	0	0.735451	7.705585	25.40692	54.50115	98.4756	176.2989	203.9003	225.7557	264.9757	283.2

Methods - Epidemiology

- Data analyses
  - Expected number of cases based on the total number of PYRS of observation was computed
  - Observed number of breast and total cancer cases divided by expected number provided the Standard Incidence Ratio (SIR); 95% confidence intervals computed using Poisson statistics
  - Cox proportional hazard modeling used to determine the association of occupational factors on rate of breast cancer

Methods - Exposure Assessment

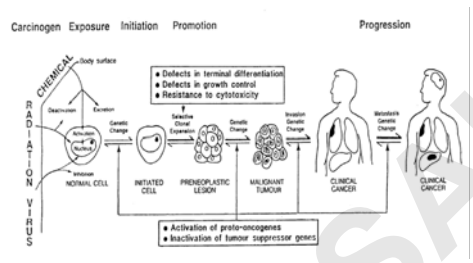
- Review of OHSAH MSDS database for chemicals and products used in hospital laboratories
- Walkthrough survey of MMHL
- Interviews with current MMHL employees
  - Changes in processes and controls over time
  - Issues with regard to air quality in MMHL over time

Methods - Literature Review

- Conducted to provide information to assist in interpretation of study findings
- Focused on breast cancer risk factors as this cancer type identified in preliminary analyses as likely with a higher incidence in MMHL employees
- Epidemiology of clusters also provided due to the complexity of the investigations that are performed to identify causal factors underlying clusters

Results - Literature Review

Carcinogenesis is a multistage process that involves many events, some of which are not well understood.



Age-adjusted Cancer Incidence in 1984-88 (US)

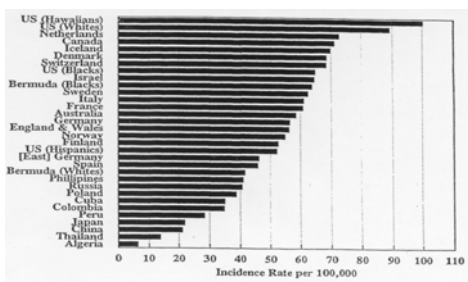
Males			Females	
1. Prostate	93.5		1. Breast	105.6
2. Lung	84.0		2. Colon/Rectum	42.9
3. Colon/Rectum	61.1		3. Lung	37.1
4. Bladder	29.9		4. Uterus	30.3
5. Lymphoma	19.1		5. Ovary	13.9
6. Mouth/ Pharynx	16.8		6. Lymphoma	13.1
7. Leukemia	13.0		7. Melanoma	9.1
8. Stomach	12.0		8. Pancreas	8.2
9. Melanoma	11.8		9. Leukemia	7.7
10. Kidney	11.4		10. Bladder	7.5
11. Pancreas	11.0		11. Mouth/Pharynx	6.5

Source: Cancer Statistics Review, 1973-1988, SEER

Breast Cancer - Demographics

- Canada one of the highest incidence rates for breast cancer (225 per 100.000 women over age 40)
- Most common malignancy in women
- Second leading cause of cancer mortality
- Lifetime risk of 1 in 9
- Most common cause of death in women 35 to 54, age of maximum social responsibility
- Average years of life lost is 19.3

Age-adjusted annual breast cancer incidence rate among women in selected countries in 1983-87.



Source: Cancer Incidence in Five Continents (IARC)

Breast Cancer Risk Factors

- 75% have none
- Age
- Family History
- Radiation exposure in childhood
- Previous malignancy (Hodgkin's)
- No children or none before 35
- Early menarche, late menopause
- Estrogen effects in breast cancer

Breast Cancer Genetics

- A small proportion of breast cancers appear to be attributable to an autosomal dominant genetic predisposition
- 5-10% of all cases
- Young age
- Strong family history
- Bilateral disease
- BRCA-1 and BRCA-2

Breast Cancer Occupational Risk Factors

- Animal studies identify mammary carcinogens
- Human studies on specific chemicals mostly equivocal
- Organochlorine compounds implicated due to estrogenic activity
- Most epidemiology studies not able to establish causal links to breast cancer
- Workers exposed to solvents at increased risk

Breast Cancer Occupational Risk Factors

- Band et al (2000) higher breast cancer rates in BC for post menopausal women in medicine, health, and nursing occupations
- Nurses have been studied and shift work is associated with increased cancer risk (suppressed melatonin production)
- A clustering of risk factors is also suspected as a cause of the observed increased risk in nursing and medical occupations

Cancer Cluster -- Epidemiology

- Regional and temporal patterns always exist
- Patterns of increased/decreased risk may be due to aggregation of diverse factors (diet, demographics, lifestyle factors, occupational exposures)
- The lower mainland of BC has a higher than average incidence of breast cancer

Cancer Cluster -- Epidemiology

- Analysis of clusters is responsibility of health agencies (BC Cancer Agency, BC CDC, Health Canada)
- Modern cancer clusters are widely reported and investigated
  - Over the last 30 years, thousands have been investigated
  - Few investigations have identified exposures etiologically related to the increase risk if an increased risk was found

Cancer Cluster -- Epidemiology

- Investigations answer questions:
  - Is the cluster real -- first report of a cluster is defined as a "perceived cluster"
  - If the cluster is real, it is termed an "observed cluster"
  - Is an agent or exposure the cause of the observed cluster -- if yes, the cluster is termed an "etiologic cluster"

Cancer Cluster -- Epidemiology

- Standard protocols for cluster investigations
  - Stepwise, going from exploratory to analytic
  - Primary objective is to identify exposures that may be increasing the risk of cancer and determining the steps to take to eliminate or reduce such risks

Cancer Cluster Epidemiology MMHL

- 57 employees working between January 1970 and August 2003
  - One person excluded from analysis
- Cancer reported: 6 breast, 1 ovarian, 1 thyroid, and 1 lymphoma in cohort
- At follow-up mean age of employees was 43.1 years
- Table 3 in report shows demographics of study cohort

Table 3. Age, gender and duration of follow-up by disease status

	No Cancer	Breast Cancer	Other Cancer	Total
Females	41 (73.21%)	6 (10.71%)	3 (5.36%)	50 (89.29%)
Males	5 (8.93%)	0	1 (1.79%)	6 (10.71%)
Mean age at start work (yrs)	29.07 (8.68)	32.03 (11.29)	33.78 (7.53)	29.72 (8.86)
Mean age at end work or end study (yrs)	42.47 (10.67)	46.2 (13.24)	45.90 (7.99)	43.12 (10.70)
Mean duration of follow-up (yrs)	13.41 (8.34)	14.16 (10.50)	12.13 (8.13)	13.40 (8.41)

Data presented as frequency (percent of total), mean (standard deviation); n=56

Table 4. Person-years and distribution of all-causes cancer by calendar year for all employees

Calendar year	Person-years	Number of incidence cases	Calendar year	Person-years	Number of incidence cases
1964	0.50	0	1984	19.79	1
1965	1.00	0	1985	22.13	0
1966	1.00	0	1986	22.13	0
1967	1.00	0	1987	24.76	0
1968	1.00	0	1988	25.92	1
1969	1.00	0	1989	26.32	0
1970	1.00	0	1990	27.96	0
1971	1.00	0	1991	33.05	1
1972	1.17	0	1992	33.51	0
1973	2.00	0	1993	34.09	1
1974	2.33	0	1994	37.21	0
1975	4.35	0	1995	37.57	0
1976	5.16	0	1996	38.02	1
1977	6.30	0	1997	38.58	1
1978	8.00	0	1998	38.00	0
1979	9.59	0	1999	38.00	0
1980	13.27	0	2000	38.77	1
1981	15.06	0	2001	38.96	0
1982	17.75	0	2002	39.00	0
1983	18.42	0	2003	21.72	3
		Total	(PYRS and cases)	751.27	10

n = 56 male and female employees.

Table 5. Person-years and distribution of breast cancer by age group in women in cancer cluster study

Age group (yrs)	Number of incident cases	Person-years	Number of incident cases
15 – 19	0	1.34	0
20 – 24	0	43.95	0
25 – 29	0	100.37	0
30 – 34	0	120.91	0
35 – 39	0	112.67	1
40 – 44	0	113.25	0
45 – 49	0	83.50	1
50 – 54	0	51.58	2
55 – 59	0	25.16	0
60 – 64	0	13.49	1
65 – 69	0	5.00	0
70 – 74	0	2.58	1
Total (PYRS and cases)		673.80	6

n = 50 female employees

Table 6. Person-years and distribution of breast cancer by calendar year for women in cancer cluster study

Calendar year	Person-years	Number of incident cases	Calendar year	Person-years	Number of incident cases
1972	0.17	0	1988	22.92	0
1973	1.00	0	1989	23.32	0
1974	1.33	0	1990	25.71	0
1975	3.33	0	1991	30.43	1
1976	4.16	0	1992	32.58	0
1977	5.30	0	1993	32.99	0
1978	7.00	0	1994	33.21	0
1979	8.59	0	1995	33.57	0
1980	11.27	0	1996	35.32	1
1981	13.06	0	1997	35.38	1
1982	15.75	0	1998	35.00	0
1983	16.42	0	1999	35.00	0
1984	17.00	1	2000	35.77	0
1985	19.14	0	2001	35.96	0
1986	19.12	0	2002	36.00	0
1987	21.76	0	2003	19.98	2
		Total	(PYRS and cases)	673.80	6

n = 50 female employees.

Table 7. Observed and expected cases and age/calendar-year adjusted standardized incidence ratios (SIRs) for breast cancer (females only) and all cancers.

	Person-years	Number of subjects	Expected cancers	Observed cancers	Standard Incidence Ratio	95% Confidence Intervals
Breast Cancer	673.80	50	0.59	6	10.2	3.74-22.24
All cancers (females only)	673.80	50	1.55	9	5.8	2.66-11.02
All cancers (all subjects)	751.27	56	1.60	10	6.3	3.02-11.59

Observed Cancer Cluster at MMHL

- **The SIR if 10.2 with 95% CI of 3.74 to 22.24 indicates the women in the cohort experienced breast cancer at a rate 10 times that which was expected**
- **The SIR of 6.3 for all cancers indicated that all employees experienced a rate of cancer over 6 times that which was expected; however this was driven by the larger proportion of breast cancer cases**

Table 8. Hazard ratios and 95% confidence intervals (CIs) of breast cancer in relation to age at start of work at MMHL, position, and job status for women

Variables	Hazard Ratio	95% CI	p-value *
Age at start work (yrs)	1.07	0.97, 1.18	0.173
Position			
Technician	1.00		
Aid, clerk or ECG	0.67	0.08, 6.04	0.723
Job status			
Part time or causal	1.00		
Full time	1.45	0.14, 15.06	0.754

* p value from Cox proportional hazards model with age at start work as a continuous variable and position and job status as categorical variables.

Observed Cancer Cluster at MMHL

- **The hazard ratios from the Cox proportional hazard models were not statistically significant**
- **The occupational factors studied in this investigation were not associated with the increase incidence of cancer in the employees at MMHL**
- **The independent variables were likely too non specific to truly assess the impact of occupational exposures on breast cancer risk**

Field Investigations at MMHL

- **Walkthrough survey**
  - **Current chemical exposures are minimal due to use of sealed systems which minimizes handling**
  - **Volumes of chemicals handled are minimal**
  - **Exposures to physical agents such as heat, noise, RF radiation appear to be minimal**
  - **No significant exposures to ionizing radiation were apparent at the time of the survey; radioisotopes are seldom, if ever used, and IR sources are not present in the laboratory**

Field Investigations at MMHL

- **Walkthrough survey**
  - **Past exposures to carcinogens was likely although the exposures levels are unknown**
  - **Formaldehyde in formalin is a known carcinogen**
  - **O-toluidine, a rat mammary carcinogen, was a potential exposure in the past (sample preparation)**
  - **Poor indoor air quality may have lead to exposures to chemical carcinogens in the past (emissions from a hospital incinerator as well as roofing emissions were reported)**

Recommendations for Further Action

- **Conduct a thorough chemical inventory and identify exposures to hazards compounds and use of any carcinogens and possible mammary carcinogens**
- **Conduct detailed exposures studies if hazardous chemical exposures are possible**
- **Ensure exposures to all forms of ionizing radiation are at background**
- **Provide information about risk factors for cancer to all MMHL employees**

Recommendations for Further Action

- **The finding of this study provide support for an observed cancer cluster but the factor(s) responsible for the cluster are unknown**
  - **It is unlikely than a more extensive epidemiology study will identify an occupational/environmental risk factor that is causally related to the increased rate -- this is due to small sample size and the difficulties with confounding, effect modification, and other statistical issues**

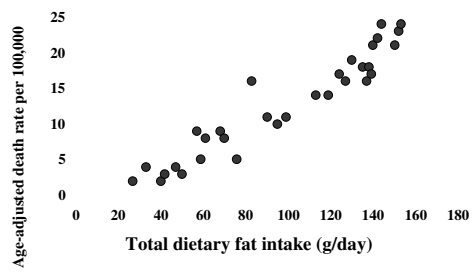
Recommendations for Further Action

- **It is recommended that a system be set up to continue the collection and linkage of employment data with cancer reports among employees of MMHL -- if subsequent analyses indicate that the SIR remains very highly elevated then further investigation is warranted**

Recommendations for Further Action

- **To further examine the likelihood of an occupational risk factor being associated with the elevated SIR, a number of actions are possible**
  - **Confirm cancer diagnoses with the BC Cancer Registry**
  - **Collect information on known breast cancer risk factors to determine if they are more or less prevalent as compared to other populations**

Correlation between breast cancer mortality rates and per capita consumption levels of fat (Ecologic comparisons)



Genetic Mutations

- Account for only 5-10% of all breast cancer cases
  - BRCA-1
  - BRCA-2

BRCA Mutations

- **BRCA-1 positive**
  - 50-80% chance breast cancer over a lifetime.
  - ovarian cancer
  - colon and prostate cancer.
- **BRCA-2 positive**
  - 50-80% chance breast cancer over lifetime
  - Less risk for ovarian cancer than BRCA1
  - Males at increased risk for breast cancer

AJCC Staging System

- T (Tumor)
- N (Nodes)
- M (Metastases)

TNM System for Breast Cancer

- **Tis** Ductal carcinoma in situ
- **T1** Tumor 2 cm or less
  - T1a 0.5 cm or less
  - T1b 1 cm or less and more than 0.5 cm
  - T1c More than 1 cm and not more than 2 cm
- **T2** Tumor 5 cm or less & more than 2 cm
- **T3** Tumor more than 5 cm
- **T4** Tumor extends to skin or chest wall
  - T4a Extension to chest wall
  - T4b Edema/ulceration/satellite nodules
  - T4c Both T4a and T4b
  - T4d Inflammatory breast carcinoma

TNM System for Breast Cancer

- **Nx** Regional nodes cannot be assessed
- **N0** Regional nodes not involved
- **N1** Metastasis to movable axillary node (s) /1-3 positive
- **N2** Metastases to ipsilateral axillary lymph nodes/4-9 positive
- **N3** Metastases to internal mammary nodes/10+ , infra or supraclavicular

White = 5th edition; yellow = 6th edition

AJCC Breast Cancer Stage

Stage	Criteria
0	Tis
I	T1 N0 M0
II	T2 or N1
III	T3N1 or T4 or N2-3
IV	M1

Breast Cancer 5 Yr Survival

- Stage 0 >95%
- Stage I 85%
- Stage II 65%
- Stage III 40%
- Stage IV 10%

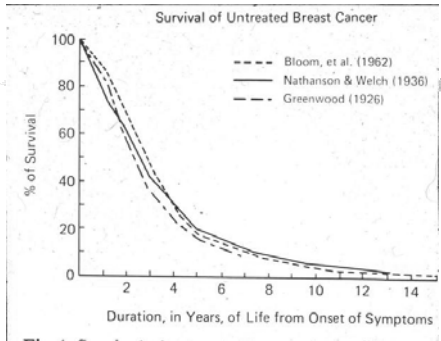


Fig. 1. Survival of untreated breast cancer. (Curves: Bloom *et al.*;[2] Greenwood;[19] Nathanson and Welch.[27]) Courtesy of *British Medical Journal*.

Attachment 5

Indoor Air Quality Assessment - Mission Memorial Hospital - Laboratory

fraserhealth Better health. Best in health care.

Indoor Air Quality Assessment - Mission Memorial Hospital - Laboratory

Walk-through survey made November 12, 2004 - 13:34-14:05

Assessment by: Dave Buhr Safety Consultant Fraser Health.

The following indoor air quality parameters were sampled

CO2 - Carbon Dioxide
Measured range - 462 PPM to 530 PPM
Assessment - **Good Fresh Air Exchange**
WCB max. for acceptable IAQ is 1000 PPM (650 PPM above outside ambient level assumed to be 350 PPM)
Health Canada recommendation is 850 PPM Max.

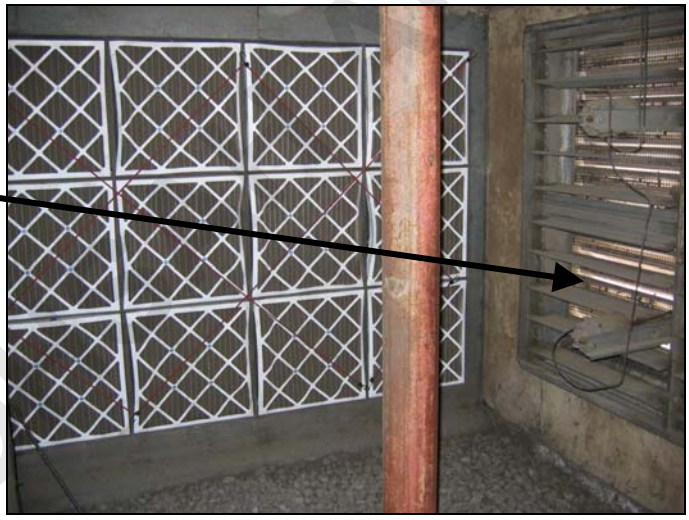
CO - Carbon Monoxide - Measured Range 0 to1 PPM
Assessment - **Good**
WCB/ACGIH TLV - 8-hr Time Weighted Average (TWA) 25 PPM

Relative Humidity - Measure Range - 26.1% to 28.3%
Assessment - **Acceptable** - below 25% staff may experience dryness of eyes, nose & throat
ASHRAE Recommended Range - 25%-60%

Temperature
21.2 C to 22.7 C
Assessment - **Normal**
Health Canada Recommendation - 80% staff comfort level

- No exterior air contaminant or exhaust discharges of concern were identified within 30 feet of the West Wing air intake when surveyed in August 2004. See attached photos.
- No interior air contaminant sources of concern were identified within the lab when surveyed August 2004. If formalin dispensing begins again in the pathology frozen section room this area should be re-evaluated for acceptable local exhaust ventilation performance.
- Nov 8/04 - Dennis Kruger (MMH - Power Engineer) and John Senetza inspected a typical supply and exhaust duct in the lab. The supply duct was clean with no evidence of dust. The inner exhaust louver intake and duct had a fine layer of dust on it. Further up the duct, there was little evidence of dust or dirt. The DNT Fan System supplies the Lab, Emergency, Health Records and two X-ray rooms.
- Last lab air balancing report - 1980 - 9 air changes per hour 4,570 CFM supply/5,068 CFM exhaust
- DNT Fan System filtration level - 85% efficiency - filter change out scheduled every 6 months or sooner as needed.

Exterior View West Wing Intake



Interior View of West Wing Intake

Attachment 6

Letter from Dave Morley
Head, Environmental Radiation Assessment Programs
Radiation Protection Services
At the BC Centre for Disease Control

BC Centre for Disease Control
AN AGENCY OF THE PROVINCIAL HEALTH SERVICES AUTHORITY

September 13, 2004

Quinn Danyluk, MSc.
Occupational Hygienist,
Workplace Safety and Wellness
Fraser Health Authority

Dear Mr. Danyluk:

Thanks for your assistance setting up and retrieving the TLD monitors at the Laboratory working area in Mission Memorial Hospital in Mission B.C. The following table contains the results.

RADIATION EXPOSURE IN THE M.M.H. LABORATORY			
Chip Number	**Location**	**Exposure in mSv.**	**2 Std. Dev. In mSv**
47	Pathologist Office	0.025	0.041
41	Microbiology	0.138	0.056
16	Outpatient Area near Exit B	0.143	0.050
11	Bloodbank	0.190	0.062
50	Chemistry Wall	0.109	0.026
42	Exit C	0.098	0.028
49	WC near Lab Directors Office	0.063	0.032
43	Hematology near Exit D	0.124	0.014
14	Control Administration Area (different building)	0.103	0.036
45	Field Control	0.109	0.038

The chips were exposed in the laboratory area for 70 days between June 18, 2004 and August 26, 2004. A typical natural background exposure for the Fraser Valley area during that period would be 0.12 mSv. I would conclude that the exposures measured

. . . /2

Radiation Protection Services
Main Floor, 655 12th Ave W
Vancouver, British Columbia
Canada V5Z 4R4

Tel 604.660.6633
Fax 604.660.6628
www.bccdc.org

in the Mission Memorial Laboratory Area are typical natural background and that the X–ray facility is not contributing to this natural background. This natural background radiation would not contribute measurably to increased cancer risk.

Yours sincerely,

Dave Morley
Head, Environmental Radiation Assessment Programs
Radiation Protection Services

k:\inbasket\trs\data\dm\Mission Hospital Radiation Exposure-Lab.doc

Attachment 7

Fraser Health
Mission Memorial Hospital Laboratory:
Chemical Assessment for Carcinogens

fraserhealth
Workplace Safety & Wellness

Mission Memorial Hospital Laboratory: Chemical Assessment for Carcinogens

SCOPE

This assessment was conducted in response to a cancer cluster within the Laboratory department at Mission Memorial Hospital. An assessment conducted by Bigelow et al (2004) recommended an assessment of chemical and radiation hazards within the department that may have carcinogenic potential. Bigelow et al provided a list of chemical substances known to have the potential of causing mammary tumors.

This report focuses on assessing the potential carcinogenicity of the current chemical products used within this department.

BACKGROUND

Quinn Danyluk (Occupational Hygienist) and Dave Buhr (Safety Consultant) conducted walkthrough surveys of the laboratory department at Mission Memorial Hospital On June 3rd, June 18th, and July 23rd.

Following these walkthrough surveys, a thorough review of the chemical products currently in use occurred. The material safety data sheets (MSDSs) were reviewed to determine if any substances within the products were carcinogenic. Rita Ciconte (Occupational Hygienist) participated in this review and summary assessment.

ASSESSMENT OF CARCINOGENICITY

The effect of a substance depends on:

1. Properties and Toxicity of the Substance
2. Dose and Concentration
3. Duration of Exposure
4. Route of Entry into the Body
5. Transport, Transformation, Distribution, and Elimination in the Body
6. Half-Life
7. Time

Carcinogenicity was determined through the use of the International Agency for Research on Cancer (IARC) Monographs. The terms utilized by IARC and throughout this review are provided below with their associated definition.

DEFINITIONS

***Group 1**: The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.*

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

***Group 2A**: The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.*

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

***Group 2B**: The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.*

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

***Group 3**: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents, mixtures and exposure circumstances for which the *evidence of carcinogenicity is inadequate* in humans and *inadequate or limited* in experimental animals. Exceptionally, agents (mixtures) for which the *evidence of carcinogenicity is inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.
Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

***Group 4**: The agent (mixture) is probably not carcinogenic to humans.*

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

Antifoam

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Silica (CAS 68855-54-9)**	**<30**	**Group 3**
	Octamethylcyclotetrasiloxane (CAS 556-67-2)	>1.0	Not Applicable
	Crystalline Silica (CAS 14464-46-1);	**>1.0**	**Group 1**
	Methylated silica (CAS 67762-90-7)	>20	Not Applicable

Exposure Limits

- Silica/Crystalline Silica: TWA 4 mg/m^3 (total); TWA 1.5 mg/m^3 (respirable)

Evaluation

Crystalline silica and silica are Group 1 and Group 3 carcinogens, respectively. Their carcinogenic potential is based upon inhalation of the substance in its particulate form. When contained within an aqueous solution, the risk of inhaling silica particulate is extremely low to impossible. Additionally, very low quantities of the product are used on an infrequent basis – a few drops may be used occasionally in the ABL 700 Blood/Gas Machine. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

Anti Seize Lubricant

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Mineral Oil (CAS 64742-52-5)**	**>60**	**Group 1**
	Lithium Soap (CAS 7620-77-1)	<3.0	Not Applicable
	Aluminum (CAS 7429-90-5)	<0.1	Not Applicable
	Copper (CAS 7440-50-8)	<0.1	Not Applicable
	Graphite (CAS 7782-42-5);	<0.1	Not Applicable
	Silica gel	<0.1	Not Applicable

Exposure Limits

- Mineral Oil: TWA 0.2 mg/m^3

Evaluation

Mineral oil (if mildly refined) is a Group 1 carcinogen. Their carcinogenic potential is based upon inhalation of the substance in a mist form. Under current usage, the potential for the generation of mist is extremely low to impossible. Additionally, very low quantities of the product are used as a lubricant for the centrifuge. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

AST (Aspartame Aminotransferase) Reagent

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Tris(hydroxymethyl) aminomethane (CAS 77861)	<3.0	Not Applicable
	Ethylene Glycol (CAS 107211)	>75.0	Not Applicable
	Sodium Azide (CAS 26628-22-8)	<0.1	Not Applicable
	Sodium hydroxide (CAS 1310-73-2)	<0.1	Not Applicable
	Glycerol (CAS 56-81-5)	>25%	Not Applicable
	Acetaldehyde (CAS 75-07-0)	**<0.1**	**Group 2B**
	Ethylene oxide (CAS 75-21-8)	**<0.1**	**Group 1**
	1,4-Dioxane (CAS 123-91-1)	<0.1	Not Applicable

Exposure Limits

- Acetaldehyde: Ceiling 25 ppm
- Ethylene oxide: TWA 0.1 ppm; STEL 1 ppm

Evaluation

Ethylene oxide is a Group 1 carcinogen; acetaldehyde is a Group 2B carcinogen. Ethylene oxide is a gas at room temperature and although used in small quantities in the production of this product, it not present in the product. Both substances comprise <0.1% of the product and are therefore not reportable as a hazardous product on the MSDS.

The product is used in the Beckman Coulter Synchron CX& Pro Clinical System where three compartments are mixed together. Acetaldehyde is present in very low concentrations and the risk of vapour generation is very low. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

B-5 Base

Manufacturer	Ingredients	Percent	Carcinogenicity
BDH	**Mercuric chloride (CAS 7487-94-7)**	**5-10**	**Group 3**

Exposure Limits

- Mercuric chloride: Not applicable

Evaluation

Mercuric chloride is a Group 3 carcinogen. It is pre-poured and mixed with 40% formaldehyde. Currently the product is not in use. If in use it should be located under local exhaust ventilation. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

Basic Fuchsin Stain Solution

Manufacturer	Ingredients	Percent	Carcinogenicity
PML	**Basic fuchsin (CAS 632-99-5)**	**0.1**	**Group 2B**
	Ethanol (CAS 64-17-5)	10.0	Not Applicable

Exposure Limits

- Basic fuchsin: Not applicable

Evaluation

Basic fuchsin is a Group 2B carcinogen. It is used as a gram stain. Basic fuchsin comprises approximately 0.1% of the stain solution. Very small quantities of the product are utilized at any given time. The potential for vapour generation is very low. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

BUN (Blood Urea Nitrogen) Reagent

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Glycerol (CAS 56815)	>1.0	Not Applicable
	Ethylene glycol (CAS 107211)	>25	Not Applicable
	Glycerine, N,N-bis(carboxymethyl)- (CAS 139-13-9)	**<0.1**	**Group 2B**

Exposure Limits

- Glycerine, N,N-bis(carboxymethyl)-: Not applicable

Evaluation

Glycerine, N,N-bis(carboxymethyl)- is a Group 2B carcinogen. The substances carcinogenic potential is based upon inhalation of the substance in its particulate form (i.e. salt form). The substance is not utilized in particulate form in the reagent. Additionally, the substance comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS.

The reagent is used in the Beckman Coulter Synchron CX7 Pro Clinical System - two compartments (A and B) that are mixed together.

- The carcinogenic potential of the product under current usage is **LOW**.

CO_2 Alkaline Buffer

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Glycine,N,N-bis(carboxymethyl)- (CAS 139-13-9);**	**<0.1**	**Group 2B**
	Polyoxyethylated Octyl Phenol (CAS 26027-38-3)	<0.1	Not Applicable

Exposure Limits

- Glycerine, N,N-bis(carboxymethyl)-: Not applicable

Evaluation

Glycerine, N,N-bis(carboxymethyl)- is a Group 2B carcinogen. The substances carcinogenic potential is based upon inhalation of the substance in its particulate form (i.e. salt form). The substance is not utilized in particulate form in the reagent. Additionally, the substance comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS.

The reagent is used in the Beckman Coulter Synchron CX7 Pro Clinical System – container is opened and placed on the instrument.

- The carcinogenic potential of the product under current usage is **LOW**.

Dade Behring CTNI Troponin Test Pack

Manufacturer	Ingredients	Percent	Carcinogenicity
Dade Behring	Bovine Serum Albumin (CAS 9048-46-8)	6	Not Applicable
	Sodium Azide (CAS 26628-22-8)	0.1	Not Applicable
	Streptomycin Sulphate (CAS 3810-74-0)	0.025	Not Applicable
	Chloramphenicol (CAS 56-75-7)	**0.000016**	**Group 2A**

Exposure Limits

- Chloramphenicol: Not applicable

Evaluation

Chloramphenicol is a Group 2A carcinogen. It is present in extremely low concentrations within the test pack (anything less than 0.1% is not reportable as a hazardous product on the MSDS). It is used in the Dade Behring Stratus CS as an in vitro diagnostic test for the measurement of cardiac troponin-I in heparinized whole blood/plasma. The product is used within a sealed container.

- The carcinogenic potential of the product under current usage is **LOW**.

Coluter Clenz Cleaning Agent

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Ethylene Oxide (CAS 75-21-8)**	**<0.1**	**Group 1**
	Ethylene Glycol Monobutyl Ether (CAS 111-76-2)	**<0.1**	**Group 3**
	1,4-Dioxane (CAS 123-91-1)	**<0.1**	**Group 2B**
	Sodium Hydroxide (CAS 1310-73-2)	<0.1	Not Applicable
	Phosphoric Acid is (CAS 7664-38-2)	<0.1	Not Applicable
	Magnesium Nitrate (CAS 10377-60-3)	<0.1	Not Applicable
	Magnesium Chloride (CAS 7786-30-3)	<0.1	Not Applicable
	Propylene Glycol (57-55-6)	<0.1	Not Applicable
	Subtilisin (9014-01-1)	<0.1	Not Applicable

Exposure Limits

- Ethylene oxide: TWA 0.1 ppm; STEL 1 ppm
- Ethylene Glycol Monobutyl Ether: TWA 20 ppm
- 1,4-Dioxane: TWA 20 ppm

Evaluation

Ethylene oxide is a Group 1 carcinogen; Ethylene Glycol Monobutyl Ether is a Group 3 carcinogen; 1,4-Dioxane is a Group 2B carcinogen. All of these substances comprise <0.1% of the product and are therefore not reportable as a hazardous product on the MSDS. Ethylene oxide is a gas at room temperature and although used in small quantities in the product production, it not present in the product.

The product is used in Beckman Coulter HmX. Product is in sealed container that is placed in instrument. Product is also placed in a squeeze bottle for cleaning the instrument.

- The carcinogenic potential of the product under current usage is **LOW**.

Diff A^C-T Tainer

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Formaldehyde (CAS 50-00-0)**	**<0.1**	**Group 1**
	Sodium sulfate	<0.1	Not Applicable
	Ethylene Oxide (CAS 75-21-8)	**<0.1**	**Group 1**
	Ethylene Glycol Monobutyl Ether (CAS 111-76-2)	**<0.1**	**Group 3**
	1,4-Dioxane (CAS 123-91-1)	**<0.1**	**Group 2B**
	Sodium Hydroxide (CAS 1310-73-2)	<0.1	Not Applicable
	Phosphoric Acid is (CAS 7664-38-2)	<0.1	Not Applicable
	Magnesium Nitrate (CAS 10377-60-3)	<0.1	Not Applicable
	Magnesium Chloride (CAS 7786-30-3)	<0.1	Not Applicable
	Propylene Glycol (57-55-6)	<0.1	Not Applicable
	Isopropyl alcohol (CAS 67-63-0)	<2	Not Applicable
	Potassium cyanide (CAS 151-50-8)	<0.1	Not Applicable
	Quaternary ammonium salt	<2	Not Applicable

Exposure Limits

- Formaldehyde: TWA 0.3; Ceiling 1 ppm
- Ethylene oxide: TWA 0.1 ppm; STEL 1 ppm
- Ethylene Glycol Monobutyl Ether: TWA 20 ppm
- 1,4-Dioxane: TWA 20 ppm

Evaluation

Formaldehyde is a Group 1 carcinogen; Ethylene oxide is a Group 1 carcinogen; Ethylene Glycol Monobutyl Ether is a Group 3 carcinogen; 1,4-Dioxane is a Group 2B carcinogen. All of these substances comprise <0.1% of the product and are therefore not reportable as a hazardous product on the MSDS. Ethylene oxide is a gas at room temperature and although used in small quantities in the product production, it not present in the product.

The product is used in the Beckman Coulter A^C-T diff 2 equipment – it is in sealed container that is placed in the instrument. The potential for exposure is very low.

- The carcinogenic potential of the product under current usage is **LOW**.

Eosin

Manufacturer	Ingredients	Percent	Carcinogenicity
Sigma	**Eosin (CAS 17372-87-1)**		**Group 3**

Exposure Limits

- Eosin: Not applicable

Evaluation

Eosin is a Group 3 carcinogen. Its carcinogenic potential is based upon oral or subcutaneous of the substance in its particulate form (i.e. salt). The potential for exposure through either route is very low. Additionally, small quantities of the product is utilized. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

Erada Stain

Manufacturer	Ingredients	Percent	Carcinogenicity
Cambridge Diagnostics	Ethanol (CAS 64-17-5)	5-15	Not Applicable
	Methanol (CAS 67-56-1)	<0.5	Not Applicable
	Triethanolamine (CAS 102-71-6)	**1-5**	**Group 3**

Exposure Limits

- Triethanolamine: TWA 5 mg/m^3

Evaluation

Triethanolamine is a Group 3 carcinogen. Its carcinogenic potential is based upon oral or subcutaneous exposure – the potential for either is low based on current usage. The risk of inhalation exposure is also very low due to small quantities of the product and low risk of vapour generation. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

Fisher Permount

Manufacturer	Ingredients	Percent	Carcinogenicity
Fisher	**Toluene (CAS 108-88-3)**	**55.17**	**Group 3**
	Piccolyte (CAS 68240-09-5)	44.85	Not Applicable

Exposure Limits

- Toluene: TWA 50 ppm

Evaluation

Toluene is a Group 3 carcinogen. The risk of exposure through the inhalation route is extremely low due to small quantities of the product and low risk of vapour generation Risk of exposure through the oral or subcutaneous route is also low. Additionally, small quantities of the product is utilized. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

Gastroccult Developer

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Hydrogen Peroxide (CAS 7722-84-1)**	**<5**	**Group 3**
	Citric acid (CAS 77-92-9)	<5	Not Applicable
	Octylphenoxypoly(ethoxyethanol) (CAS 9036-19-5)	<5	Not Applicable
	Ethanol-methanol mix (CAS 8013-52-3)	<50	Not Applicable
	Ethylene Oxide (CAS 75-21-8)	**<0.1**	**Group 1**
	1,4-Dioxane (CAS 123-91-1)	**<0.1**	**Group 2B**

Exposure Limits

- Hydrogen peroxide: TWA 1 ppm
- Ethylene oxide: TWA 0.1 ppm; STEL 1 ppm
- 1,4-Dioxane: TWA 20 ppm

Evaluation

Hydrogen peroxide is a Group 3 carcinogen; Ethylene oxide is a Group 1 carcinogen; 1,4-Dioxane is a Group 2B carcinogen.

Ethylene oxide is a gas at room temperature and although used in small quantities in the product production, it not present in the product. 1,4-Dioxane showed potential risk of carcinogenicity following oral exposure in rats and mice but not following inhalation exposure – the risk of oral exposure is very low. Ethylene oxide and 1,4-Dioxane comprise <0.1% of the product and are therefore not reportable as a hazardous product on the MSDS.

This product is rarely used. When it is used a drop is placed on a slide with blood. Very low quantities are used; the risk of exposure through any route is very low. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

HCL 0.1%

Manufacturer	Ingredients	Percent	Carcinogenicity
RCH	**Hydrochloric acid (CAS 7647-01-0)**	**0.1**	**Group 3**

Exposure Limits

Hydrochloric acid: Ceiling 2 ppm

Evaluation

Hydrochloric acid is a Group 3 carcinogen and thus is not classifiable with respect to human carcinogenicity. This product is used in urinalysis crystal solubility. The quantity, concentration, method of use, and exposure potential is sufficiently low to classify as a low risk.

- The carcinogenic potential of the product under current usage is **LOW**.

HCL 25%

Manufacturer	Ingredients	Percent	Carcinogenicity
RCH	**Hydrochloric acid (CAS 7647-01-0)**	**25**	**Group 3**

Exposure Limits

Hydrochloric acid: Ceiling 2 ppm

Evaluation

Hydrochloric acid is a Group 3 carcinogen and thus is not classifiable with respect to human carcinogenicity. This product is used to preserve 24 hour urine. Low quantities of the product are used. The potential for exposure through inhalation is low. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

Hemocult SENSA Developer

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Ethanol (CAS 64-17-5)	80	Not applicable
	Hydrogen peroxide (CAS 7722-84-1)	**<4.2**	**Group 3**

Exposure Limits

- Hydrogen peroxide: TWA 1 ppm

Evaluation

Hydrogen peroxide is a Group 3 carcinogen. Very low quantities of the product are used. The solution is dropped onto a card. The potential for exposure through any route is very low.

- The carcinogenic potential of the product under current usage is **LOW**.

Hydrox 7

Manufacturer	Ingredients	Percent	Carcinogenicity
Virox	3-Methoxy-3-methyl butanol (CAS 56539-66-3)	3-7	Not applicable
	Hydrogen peroxide (CAS 7722-84-1)	3-7	**Group 3**

Exposure Limits

- Hydrogen peroxide: TWA 1 ppm

Evaluation

Hydrogen peroxide is a Group 3 carcinogen. This product is used for cleaning chairs and benches; the minimum recommended quantity of product should be used whenever performing these tasks so as to minimize exposure. The product contains low quantities of hydrogen peroxide. Hydrogen peroxide has a low vapour pressure (<0.1 kPa); as a result, airborne exposure potential is low. Its carcinogenic potential is based upon oral or subcutaneous exposure – the potential for either is low based on current usage. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

ISE Electrolyte Buffer

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Maleic Acid <5% (CAS 110-16-7)	<5	Not applicable
	Tris(hydroxymethyl)aminomethane <15% (CAS 77-86-1)	<15	Not applicable
	Methanol <0.1% (CAS 67-56-1)	<0.1	Not applicable
	Formaldehyde <0.1% (CAS 50-00-0)	**<0.1**	**Group 1**

Exposure Limits

- Formaldehyde: TWA 0.3; Ceiling 1 ppm

Evaluation

Formaldehyde is a group 2A carcinogen. Formaldehyde comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS. The quantity, concentration, method of use, and exposure potential is sufficiently low to classify as a low risk. The potential for airborne exposure is very low.

- The carcinogenic potential of the product under current usage is **LOW**.

Isoton III

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Formaldehyde (CAS 50-00-0)**	**<0.1**	**Group 1**
	Sodium sulfate (CAS 7757-82-6)	<0.1	Not applicable
	Propylene glycol (CAS 57-55-6)	<0.1	Not applicable

Exposure Limits

- Formaldehyde: TWA 0.3; Ceiling 1 ppm

Evaluation

Formaldehyde is a group 2A carcinogen. Formaldehyde comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS. The quantity, concentration, method of use, and exposure potential is sufficiently low to classify as a low risk. The potential for airborne exposure is very low.

- The carcinogenic potential of the product under current usage is **LOW**.

Javex

Manufacturer	Ingredients	Percent	Carcinogenicity
Colgate Palmolive	**Sodium hypochlorite (CAS 7681-52-9)**	**5-10**	**Group 3**

Exposure Limits

- Sodium hypochlorite: Not applicable

Evaluation

Sodium hypochlorite is a group 3 carcinogen. Its carcinogenic potential is based upon oral exposure of the salt (particulate form); exposure via the skin has not been found to result in an increase risk. The risk of oral exposure to the salt is very low based on current usage. Gloves should be worn to prevent skin contact. This product is used infrequently for equipment maintenance.

- The carcinogenic potential of the product under current usage is **LOW**.

Potassium dichromate

Manufacturer	Ingredients	Percent	Carcinogenicity
Fisher Scientific	**Chromic acid, dipotassium salt (CAS 7778-50-9)**	100	**Group 3**

Exposure Limits

- Chromic acid, dipotassium salt: Not applicable

Evaluation

Chromic acid is a Group 3 carcinogen. Its carcinogenic potential is based upon oral exposure of the salt (particulate form) – exposure potential via this route would be low. The product is used during quality control tests approximately 3 times per week. Used in the Beckman Coulter Synchron CX7 Clinical System for quality control check – done three times per week.

- The carcinogenic potential of the product under current usage is **LOW**.

S-CAL Calibrator Kit

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Treated Human Erythrocytes	45	Not applicable
	5-Fluorouracil (CAS 51-21-8)	**<0.1**	**Group 3**

Exposure Limits

- 5-Fluorouracil: Not applicable

Evaluation

5-Fluorouracil is a Group 3 carcinogen. 5-Fluorouracil comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS. Its carcinogenic potential is based upon oral and intravenous exposure – exposure potential via this route would be very low.

- The carcinogenic potential of the product under current usage is **LOW**.

Salicylate Reagent

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Chloroform (CAS 67-66-3)**	**<0.1**	**Group 2B**

Exposure Limits

- Chloroform: TWA 2 ppm

Evaluation

Chloroform is a Group 2B carcinogen. It comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS. Because of the very low concentration, the potential for exposure via any route is very low. Used in Beckman Coulter Synchron CX7 Pro Clinical System. Gloves should be worn to prevent skin contact.

- The carcinogenic potential of the product under current usage is **LOW**.

TBIL (Total Bilirubin) Reagent

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	**Caffeine (CAS 58-08-2)**	**<5**	**Group 3**
	Sodium Acetate (CAS 127-09-3)	<10	Not applicable
	Sodium Benzoate (CAS 532-32-1)	<10	Not applicable
	Ethoxylated lauryl alcohol (CAS 9002-92-0)	<0.1	Not applicable
	Hydrochloric acid (CAS 7647-01-0)	**<0.5**	**Group 3**
	Sodium nitrite (CAS 7632-00-0)	<10	Not applicable

Exposure Limits

- Caffeine: Not applicable
- Hydrochloric acid: Ceiling 2 ppm

Evaluation

Caffeine and hydrochloric acid are Group 3 carcinogens. The carcinogenicity level, potential exposure, quantity within the product, and duration and frequency of use will not result in an increase risk.

- The carcinogenic potential of the product under current usage is **LOW**.

Wash Concentrate

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Methyl P-Hydroxybenzoate (CAS 99-76-3)	3.0	Not applicable
	Ethylene oxide (CAS 75-21-8)	**<0.1**	**Group 1**

Exposure Limits

- Ethylene oxide: TWA 0.1 ppm; STEL 1 ppm

Evaluation

Ethylene oxide is a Group 1 carcinogen. Ethylene oxide is a gas at room temperature and although used in small quantities in the production of this product, it not present in the product. It comprises <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS. The quantity, concentration, method of use, and exposure potential is sufficiently low to classify this as low risk.

- The carcinogenic potential of the product under current usage is **LOW**.

Wash Concentrate II

Manufacturer	Ingredients	Percent	Carcinogenicity
Beckman	Potassium hydroxide (CAS 1310-58-3)	≥ 2%	Not applicable
	Diethanolamine (CAS 111-42-2)	**<0.1**	**Group 3**
	Triethanolamine (CAS 102-71-6)	**<0.1**	**Group 3**
	Richonic Acid B (CAS 27176-87-0)	<0.1	Not applicable

Exposure Limits

- Diethanolamine: TWA 2 mg/m^3
- Triethanolamine: TWA 5 mg/m^3

Evaluation

Diethanolamine and Triethanolamine are Group 3 carcinogens. Both substance comprise <0.1% of the product and are therefore not reportable as a hazardous product on the MSDS. Due to the very low percentages of these substances within this product, exposure potential via any route is very low. Used in Beckman Coulter Synchron CX7 Pro Clinical System – NOT mixed with water

- The carcinogenic potential of the product under current usage is **LOW**.

SUMMARY

Bigelow et al provided a list of chemical substances known to have the potential of causing mammary tumors – see below:

- ❑ Acronycine
- ❑ Benzene
- ❑ 2,2-bis(bromomethyl)- 1,3-propanediol
- ❑ 1,3-Butadiene
- ❑ C,1 acid red 114
- ❑ C,1 basic red 9 monohydrochloride
- ❑ 2-Chloroacetophenone
- ❑ Chloroprene
- ❑ Clonitralid
- ❑ Cytembene
- ❑ 2,4-Diaminotoluene
- ❑ 1,2-Dibromo-3-chloropropane
- ❑ 1,2-Dibromoethane
- ❑ Indium phosphide
- ❑ Isoprene
- ❑ Methylene chloride
- ❑ Methyleugenol
- ❑ Nithiazide
- ❑ 5-Nitroacenaphthene
- ❑ Nitrofurazone
- ❑ Nitromethane
- ❑ 1,2-Dibromo-1-propanol
- ❑ 1,1-Dichloroethane
- ❑ 1,2-Dichloroethane
- ❑ 1,2-Dichloropropane (propylene dichloride)
- ❑ Dichlorvos
- ❑ 1,2-Dimethoxybenzidine dihydrochloride
- ❑ 3,3-Dimethylbenzidine dihydrochloride
- ❑ 2,4-Dinitrotoluene
- ❑ Ethylene oxide
- ❑ Furosemide
- ❑ Glycidol
- ❑ Hydrazobenzene
- ❑ Isophosphamide
- ❑ Ochratoxin A
- ❑ Phenesterin
- ❑ Procarbazine hydrochloride
- ❑ Reserpine
- ❑ Sulfallate
- ❑ 2,4- and 2,6-Toluene diisocyanate
- ❑ *o*-Toluidine hydrochloride
- ❑ 1,2,3-Trichloropropane

Only one of these substances, ethylene oxide, was found to be present in any of the products used in the lab. In every case, the concentration of ethylene oxide was <0.1% of the product and is therefore not reportable as a hazardous product on the MSDS. Additionally, ethylene oxide is a gas at room temperature and although used in small quantities in the product production, it not present in the product. Other potential carcinogens are used in the production or are present in some of the products. These include:

Substance	Carcinogenicity
Crystalline Silica	Group 1
Mineral Oil	Group 1
Formaldehyde	Group 1
Ethylene oxide	Group 1
Chloramphenicol	Group 2A
Acetaldehyde	Group 2B
Basic fuchsin	Group 2B
Glycerine, N,N-bis(carboxymethyl)-	Group 2B
1,4-Dioxane	Group 2B
Chloroform	Group 2B
Silica	Group 3
Mercuric chloride	Group 3

Substance	Carcinogenicity
Ethylene Glycol Monobutyl Ether	Group 3
Eosin	Group 3
Triethanolamine	Group 3
Toluene	Group 3
Hydrogen Peroxide	Group 3
Hydrochloric acid	Group 3
Sodium hypochlorite	Group 3
Chromic acid, dipotassium salt	Group 3
5-fluorouracil	Group 3
Caffeine	Group 3
Diethanolamine	Group 3
Triethanolamine	Group 3

Based on current scientific knowledge none of these substances are present in a quantity or currently used in a manner that would result in potential exposure via any occupational exposure route that would result in an increased risk of cancer.

Attachment 8

AN INVESTIGATION OF A CANCER CLUSTER WITHIN THE MISSION MEMORIAL HOSPITAL LABORATORY – FINAL UPDATE

April 15, 2005

AN INVESTIGATION OF A CANCER CLUSTER WITHIN THE MISSION MEMORIAL HOSPITAL LABORATORY – FINAL UPDATE

April 15, 2005

OHSAH

Occupational Health & Safety Agency for Healthcare in BC

#301-1195 West Broadway, Vancouver, BC V6H 3X5

AN INVESTIGATION OF A CANCER CLUSTER WITHIN THE MISSION MEMORIAL HOSPITAL LABORATORY – FINAL UPDATE

March 22nd, 2005

Introduction

Since the March 2004 report of the same title, prepared by the Occupational Health and Safety Agency for Healthcare (OHSAH), a new case of breast cancer in the workforce came to light, and along with it, a request to OHSAH to re-calculate the cancer rates. This final update of the report includes such a recalculation, taking into account, of course, the additional person-years at risk that comes with extending the analysis, as well as new information on the actual number of employees at risk. This report also includes additional comments on chemical exposure and air quality assessment conducted by Workplace Health as well as comments on radiation exposure conducted by BC Centre for Disease Control (BCCDC). This was done as per the recommendations in the original report.

Epidemiology

New data

1. Another female employee was diagnosed with breast cancer December 7th of 2004; this brings the total number of cancer cases to 11: comprising 7 breast (female) and 4 other (3 female and 1 male) which affects the numerator of the incidence calculation

2. There were actually 63 employees (57 of whom were female). The original analysis included only 57 employees. This change in the employee numbers affects the denominator of the incidence calculation.

Methods

To recalculate the incidence of cancer, we have used a new censor (closure) date of December 31st 2004 (versus August 31st, 2004) to include the most recent case. We have asked the BC Cancer Agency (BCCA) to provide a data linkage for these 63 employees to ensure that there were no unreported cancer cases within this group. As this information will not be available until August of 2005 and the possibility of an unknown case is very low, we have recalculated the data using the numbers stated above (ie. 11 cases of cancer). That is, we have assumed no additional cases. In the unlikely situation that more new cases are found in the period between August and December 31st, this calculation will be re-done again.

Results

Table 1 represents disease status of the laboratory employees. Table 2 presents the new calculated incidence of cancer, both breast and other.

Interpretation

As more time has passed, the denominator (time) has increased faster than the numerator (cancer cases) and the standard incidence ratio (SIR) has in fact decreased despite the new case, for both total cancer cases (SIR = 4.70) and breast cancer cases in females (SIN = 8.43). This is likely due to the additional work hours of the 6 unidentified employees now included in the analysis. Despite this decrease, **the SIR is still significantly higher than the expected incidence in BC** for both groups (total cancer and female breast cancer), indicating that the perceived cluster is an observed (true) cluster with a high degree of confidence (95% probability that this observation was NOT due to chance alone). However the new information, when used in the Cox regression model to identify cause, continues to indicate that **age at start of work at MMHL, job position, and job status do not contribute to this cluster**.

Environmental review

1. Chemical agents: the field investigation regarding exposure did not show any obvious carcinogenic exposure in the MMH laboratory, as known from the current scientific literature (see previous report).

2. Physical agents: in September of 2004, Radiation Protection Services (BCCDC), completed an assessment of radiation exposure in the laboratory, concluding that "the exposures measured in the Mission Memorial Laboratory Area are typical natural background and that the X–ray facility is not contributing to this natural background…this natural background radiation would not contribute measurably to increased cancer risk."

3. Air Quality: Basic indoor air quality testing was performed and was shown to be within acceptable standards.

Conclusion (summary)

- The increased incidence of **breast** cancer in laboratory employees is **an observed cluster.**
- Using statistical analysis, we still conclude that this increase is not related to age at start of work, job position, or job status.
- On observation and literature review, no current occupational chemical exposures, or records of past occupational exposures were found that relate to breast cancer, or cancer in general. No significant findings were found during radiation testing in the laboratory, or on basic air quality testing.

The conclusion thus remains the same. The most likely explanation for the occurrence is a 'chance cluster' or statistical anomaly. It is recommended that this cancer cluster investigation be closed. A new cluster investigation may be considered at a future time for comparison (usually 5 years after the original investigation) using new cases and new data.

Every effort should continue to be made, in this and all workplaces, to ensure that the workplace remains as safe and free of carcinogenic exposures as possible, and that the workforce is able to pursue safe and healthy choices in all aspects of their lives.

Table 1.

Age, gender and duration of follow-up by disease status

	No Cancer	Breast Cancer	Other Cancer	Total
Females	47 (74.6%)	7 (11.1%)	3 (4.8%)	57 (90.5%)
Males	5 (7.9%)	0	1 (1.6%)	6 (9.5%)
Mean Age (yrs)	45.7 (10.8)	53.4 (8.7)	51.7 (11.4)	46.9 (10.8)
Mean duration of follow-up (yrs)	15.1 (8.0)	17.7 (9.1)	14.6 (13.1)	15.4 (8.3)

Data presented as frequency, mean (standard deviation).

Table 2.

Observed and expected cases and age/calendar-year adjusted standard incidence ratios (SIRs) for breast cancer (females only) and all cancers.

Cause	Person-years	Number of subjects	Expected cancers	Observed cancers	Standard Incidence Ratio	95% Confidence Intervals
Breast Cancer (females)	856.28	57	0.83	7	8.43	3.39 – 17.38
All cancers (females only)	856.28	57	2.18	10	4.59	2.20 – 8.44
All cancers (all subjects)	973.49	63	2.34	11	4.70	2.35 – 8.41

Table 3a. Age at start of work, age at interview, gender, mean duration of occupational exposure and mean duration of follow-up at interview by disease status for all staff working after 1982 at the Mission Memorial Hospital laboratory

Variable	No Cancer	Breast Cancer	Other Cancer	Total
Females	47 (74.6%)	7 (11.1%)	3 (4.8%)	57 (90.5%)
Males	5 (7.9%)	0	1 (1.6%)	6 (9.5%)
Age at start of work (yrs)	30.5 (9.1)	30.5 (11.1)	33.8 (7.6)	30.7 (9.1)
Age at interview (yrs)	45.7 (10.8)	54.1 (9.8)	51.8 (11.3)	47.0 (11.0)
Mean duration of follow-up (yrs)	15.1 (8.0) Median: 14.0	18.3 (9.6) Median: 16.0	14.6 (13.1) Median: 9.6	15.4 (8.3) Median: 14.1
Mean duration of occupational exposure (yrs)	9.2 (7.6) Median: 6.0	18.0 (10.6) Median: 17.8	15.6 (14.0) Median: 10.7	10.6 (8.8) Median: 7.2

Data are presented as frequency (percentage) for gender, mean (standard deviation) for age at start of work, age at interview, mean duration of follow-up and mean duration of occupational exposure.

Table 3b. Age at start of work, age at interview, gender, mean duration of occupational exposure and mean duration of follow-up at interview by disease status for female staff working after 1982 at the Mission Memorial Hospital laboratory

Variable	No Cancer	Breast Cancer	Other Cancer	Total
Females	47 (74.6%)	7 (11.1%)	3 (4.8%)	57 (90.5%)
Age at start of work (yrs)	30.6 (8.9)	30.5 (11.1)	36.7 (6.0)	30.9 (9.0)
Age at interview (yrs)	45.6 (10.8)	54.1 (9.9)	47.1 (7.9)	46.7 (10.8)
Mean duration of follow-up (yrs)	15.0 (8.2) Median: 14.0	18.3 (9.6) Median: 16.0	8.3 (2.9) Median: 8.0	15.0 (8.3) Median: 14.0
Mean duration of occupational exposure (yrs)	9.4 (7.8) Median: 6.4	18.0 (10.6) Median: 17.8	8.8 (4.3) Median: 7.8	10.4 (8.4) Median: 7.2

Data are presented as frequency (percentage) for gender, mean (standard deviation) for age at start of work, age at interview, mean duration of follow-up and mean duration of occupational exposure.

Table 4. Person-years and distribution of all-causes cancer by calendar year for all employees

Calendar year	Person-years	Number of incident cases	Calendar year	*Person-years*	*Number of incident cases*
1964	0.50	0	1985	23.14	0
1965	1.00	0	1986	24.12	0
1966	1.00	0	1987	26.76	0
1967	1.00	0	1988	28.00	0
1968	1.00	0	1989	29.98	0
1969	1.00	0	1990	32.71	0
1970	1.00	0	1991	38.05	1
1971	1.00	0	1992	40.66	0
1972	1.17	0	1993	42.19	1
1973	2.29	0	1994	44.17	0
1974	3.33	0	1995	46.32	1
1975	5.35	0	1996	46.51	1
1976	6.16	0	1997	47.34	0
1977	7.30	0	1998	48.91	1
1978	8.50	0	1999	49.54	0
1979	9.59	0	2000	53.04	1
1980	12.77	0	2001	55.77	1
1981	15.06	0	2002	54.71	2
1982	17.26	0	2003	53.16	1
1983	18.42	0	2004	52.90	1
1984	20.79	0			
	Total			973.49	

n = 63 male and female employees

Table 5. Person-years and distribution of breast cancer by age group in women in cancer cluster study

Age group (yrs)	Number of incident cases	*Person-years*	*Number of incident cases*
15 – 19	0	1.34	0
20 – 24	0	44.47	0
25 – 29	0	120.18	0
30 – 34	0	150.75	0
35 – 39	0	145.25	2
40 – 44	0	132.74	1
45 – 49	0	106.07	1
50 – 54	0	71.48	1
55 – 59	0	45.49	1
60 – 64	0	22.00	0
65 – 69	0	12.49	1
70 – 74	0	4.00	0
Total		856.28	

n = 57 female employees

Table 6. Person-years and distribution of breast cancer by calendar year for women in cancer cluster study

Calendar year	Person-years	Number of incident cases	Calendar year	*Person-years*	Number of incident cases
1972	0.17	0	1989	26.32	0
1973	1.29	0	1990	28.71	0
1974	2.33	0	1991	33.43	1
1975	4.35	0	1992	35.66	0
1976	5.16	0	1993	37.19	0
1977	6.30	0	1994	39.17	0
1978	7.50	0	1995	41.32	1
1979	8.59	0	1996	40.86	1
1980	11.27	0	1997	41.34	0
1981	13.06	0	1998	43.42	0
1982	15.26	0	1999	44.54	0
1983	16.42	0	2000	48.04	0
1984	18.00	0	2001	50.77	1
1985	20.14	0	2002	49.71	1
1986	21.12	0	2003	48.16	1
1987	23.76	0	2004	47.90	1
1988	25.00	0			
	Total			856.28	

n = 57 female employees

Table 7. Observed and expected cases and age/calendar-year adjusted standard incidence ratios (SIRs) for breast cancer (females only) and all cancers.

Cause	Person-years	Number of subjects	Expected cancers	Observed cancers	Standard Incidence Ratio	95% Confidence Intervals
Breast Cancer (females)	856.28	57	0.83	7	8.43	3.39 – 17.38
All cancers (females only)	856.28	57	2.18	10	4.59	2.20 – 8.44
All cancers (all subjects)	973.49	63	2.34	11	4.70	2.35 – 8.41

Table 8. Hazard ratios (HR) and 95% confidence intervals (CIs) of breast cancer for women in relation to age at start of work, position and occupational exposure at MMHL

Variable	Hazard Ratio (HR)	95% CI	p-value *
Age at start of work (yrs)	1.07	0.95 – 1.21	0.264
Occupational exposure (yrs)	1.03	0.92 – 1.15	0.581
Position			
Aid, clerk or ECG technician	1.00		
Technician	4.24	0.36 – 49.38	0.249

MMHL = the Mission Memorial Hospital Laboratory.

*, p-value was derived from Cox proportional hazards model with age at start of work and year of occupational exposure as continuous variables and position as a categorical variable.

Attachment 9

An Investigation of a Cancer Cluster within a Hospital Laboratory - report regarding the cancer cluster at Mission Hospital, Fraser Health, BC. Presentation: March 2005

An Investigation of a Cancer Cluster within a Hospital Laboratory final report regarding the cancer cluster at Mission Hospital, Fraser Health, BC.

Introduction

- Report of seemingly high number of cancer cases in laboratory workers
- Need for an epidemiological study
- Purpose of investigation:
  - To determine if cluster had occurred
  - To identify possible occupational factors if a true cluster is identified
  - To ensure current exposures/occupational factors are below recommended standards and current exposures are not increasing the risk of cancer in MMHL employees

Methods - Epidemiology

- Defined occupational cohort
  - Employee data files for all individuals working from 1970 to 2003
- Analysis of cancer incidence data
  - Collection of data on health status and cancer incidence from personal interviews (57)
  - Data entered into excel and SPSS
  - Rates of cancer and breast cancer from 1970 to 2002 for males and females obtained
  - Person years of observation (PYRS) were computed for study cohort for each age interval (5 yr increments) and calendar year
  - Expected number of cases (breast and all cancers) computed for each age and calendar year category

Methods - Epidemiology

- Data analyses
  - Expected number of cases based on the total number of PYRS of observation was computed
  - Observed number of breast and total cancer cases divided by expected number provided the Standard Incidence Ratio (SIR); 95% confidence intervals computed using Poisson statistics *(to see if an apparent high incidence is a chance findings)*
  - Cox proportional hazard modeling used to determine the association of occupational factors on rate of breast cancer *(for example whether there is a relationship between duration of time at work and cancer rate)*

Methods - Exposure Assessment

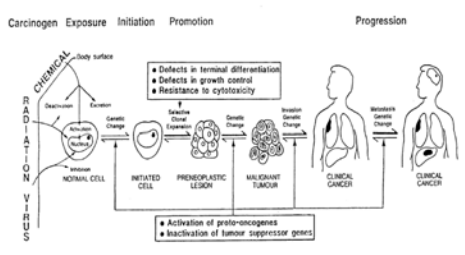
- Review of OHSAH MSDS database for chemicals and products used in hospital laboratories
- Walkthrough survey of MMHL
- Interviews with current MMHL employees
  - Changes in processes and controls over time
  - Issues with regard to air quality in MMHL over time

Methods - Literature Review

- Conducted to provide information to assist in interpretation of study findings
- Focused on breast cancer risk factors as this cancer type identified in preliminary analyses as likely with a higher incidence in MMHL employees

Results - Literature Review

Carcinogenesis is a multistage process that involves many events, some of which are not well understood.



Cancer Incidence in British Columbia (2003)

Males		Females	
Prostate	125.15	Breast	118.1
Lung	63.8	Lung	54.4
Colon/rectum	60.3	Colon/rectum	51.6
Lymphoma	22.1	Uterus	23.9
Melanoma	18.0	Lymphoma	18.1
Bladder	17.1	Melanoma	13.7
Mouth/Pharynx	14.1	Ovary	12.8
Kidneys	12.5	Pancreas	11.5
Leukemia	11.7	Leukemia	8.2
Stomach	10.5	Mouth/Pharynx	6.0
Pancreas	10.4	Bladder	5.7

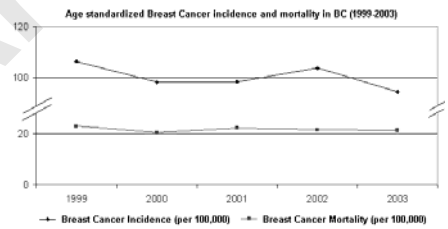
Source: BCCA Cancer Statistics 2003

Cancer Mortality in 2003 in British Columbia

Males		Females	
Lung	54.9	Lung	44.2
Prostate	21.4	Breast	29.2
Colon/rectum	21.2	Colon/rectum	16.7
Pancreas	10.9	Ovary	11.7
Lymphoma	8.3	Pancreas	11.2
Leukemia	7.6	Lymphoma	7.4
Bladder	7.1	Leukemia	5.3
Stomach	6.2	Uterus	3.9
Kidneys	5.1	Bladder	2.9
Mouth/Pharynx	3.3	Melanoma	2.7
Melanoma	3.1	Mouth/Pharynx	1.8

Source: BCCA Cancer Statistics 2003

Age-adjusted Cancer Incidence and Mortality in 2003 in British Columbia



Source: BCCA Cancer Statistics 2003

Breast Cancer - Demographics

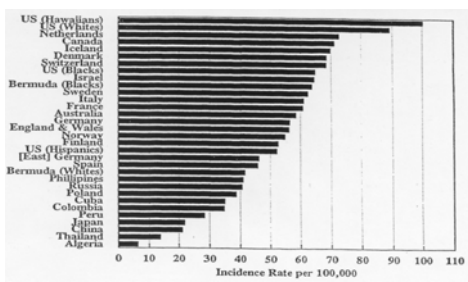
- Canada one of the highest incidence rates for breast cancer

	0-19	20-39	40-59	60-79	80+	All ages
Breast Cancer (incidence per 100,000)	**0.4**	**22.5**	**166.1**	**325.6**	**309.0**	**118.1**

BC Cancer Agency (2003)

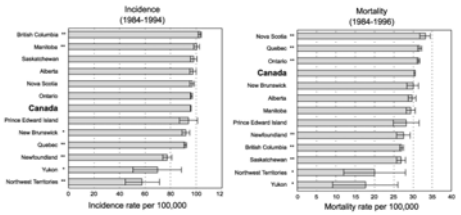
- Most common malignancy in women
- Second leading cause of cancer mortality
- Lifetime risk of 1 in 9
- Most common cause of death in women 35 to 54, age of maximum social responsibility
- Average years of life lost is 19.3

Age-adjusted annual breast cancer incidence rate among women in selected countries in 1983-87.



Source: Cancer Incidence in Five Continents (IARC)

Incidence and Mortality rates of Breast Cancer in Canada (1984-1994/1996)



Source: Cancer Bureau, Laboratory Centre for Disease Control, Health Canada, based on data supplied by Statistics Canada (April 1999)
http://www.phac-aspc.gc.ca/publicat/updates/breast-99_e.html

Breast Cancer Risk Factors

- 75% have no known risk factors
- Age
- Family History
- Radiation exposure in childhood
- Previous malignancy (Hodgkin's)
- No children or none before 35
- Early menarche, late menopause
- Estrogen effects in breast cancer

Breast Cancer Genetics

- A small proportion of breast cancers appear to be attributable to an autosomal dominant genetic predisposition
- 5-10% of all cases
- Young age
- Strong family history
- Bilateral disease
- BRCA-1 and BRCA-2

Breast Cancer Occupational Risk Factors

- Animal studies identify mammary carcinogens
- Human studies on specific chemicals mostly equivocal
- Organochlorine compounds implicated due to estrogenic activity
- Most epidemiology studies not able to establish causal links to breast cancer

Breast Cancer Occupational Risk Factors

- Band et al (2000) higher breast cancer rates in BC for post menopausal women in medicine, health (OR=1.50; CI: 1.13-1.98), and nursing (OR=1.37; CI: 1.01-1.85) occupations (***90% CI***)
- Nurses have been studied and shift work is associated with increased cancer risk (*30 or more years on the night shift: RR 1.36; 95%CI=1.04-1.78)* (suppressed melatonin production) (E. Schernhammer et al. J. National Cancer Institute 2001; Stevens R. Epidemiology 2005)
- A clustering of risk factors is also suspected as a cause of the observed increased risk in nursing and medical occupations

Cancer Cluster -- Epidemiology

- Regional and temporal patterns always exist
- Patterns of increased/decreased risk may be due to aggregation of diverse factors (diet, demographics, lifestyle factors, occupational exposures)
- The lower mainland of BC has a higher than average incidence of breast cancer

Cancer Cluster -- Epidemiology

- Analysis of clusters is responsibility of health agencies (BC Cancer Agency, BC CDC, Health Canada, OHSAH)
- Modern cancer clusters are widely reported and investigated
  - Over the last 30 years, thousands have been investigated
  - Few investigations have identified exposures etiologically related to the increase risk if an increased risk was found

Cancer Cluster -- Epidemiology

- Investigations answer questions:
  - Is the cluster real -- first report of a cluster is defined as a "perceived cluster"
  - If the cluster is real, it is termed an "observed cluster"
  - Is an agent or exposure the cause of the observed cluster -- if yes, the cluster is termed an "etiologic cluster"

Cancer Cluster -- Epidemiology

- Standard protocols for cluster investigations
  - Stepwise, going from exploratory to analytic
  - Primary objective is to identify exposures that may be increasing the risk of cancer and determining the steps to take to eliminate or reduce such risks

Cancer Cluster Epidemiology MMHL

- 57 employees working between January 1970 and August 2003
  - One person excluded from analysis (Breast Ca identified before employment)
- Cancer reported: 6 breast, 1 ovarian, 1 thyroid, 1 skin, and 1 lymphoma in cohort
- At follow-up mean age of employees was 43.1 years

Age, gender and duration of follow-up by disease status

	No Cancer	Breast Cancer	Other Cancer	Total
Females	**41** (73.21%)	**6** (10.71%)	**3** (5.36%)	**50** (89.29%)
Males	**5** (8.93%)	**0**	**1** (1.79%)	**6** (10.71%)
Mean age at start work (yrs)	**29.07** (8.68)	**32.03** (11.29)	**33.78** (7.53)	**29.72** (8.86)
Mean age at end work or end study (yrs)	**42.47** (10.67)	**46.2** (13.24)	**45.90** (7.99)	**43.12** (10.70)
Mean duration of follow-up (yrs)	**13.41** (8.34)	**14.16** (10.50)	**12.13** (8.13)	**13.40** (8.41)

Data presented as frequency (percent of total), mean (standard deviation); n=56

Age, gender and duration of follow-up by disease status

- **Analysis is based on the March 2004 data**

Table. Observed and expected cases and age/calendar-year adjusted standardized incidence ratios (SIRs) for breast cancer (females only) and all cancers

	Person years	Number of Subjects	Expected Cancers	Observed Cancers	Standard Incidence Ratio	95% Confidence Interval
Breast Cancer	**673.80**	**50**	**0.59**	**6**	**10.2**	**3.74-22.24**
All Cancers (Females only)	**673.80**	**50**	**1.55**	**9**	**5.8**	**2.66-11.02**
All Cancers (All Subjects)	**751.27**	**56**	**1.60**	**10**	**6.3**	**3.02-11.59**

Observed Cancer Cluster at MMHL

- **The SIR of 10.2 with 95% CI of 3.74 to 22.24 indicates the women in the cohort experienced breast cancer at a rate 10 times that which was expected**
- **The SIR of 6.3 for all cancers indicated that all employees experienced a rate of cancer over 6 times that which was expected; however this was driven by the larger proportion of breast cancer cases**

Observed Cancer Cluster at MMHL

Table. Hazard ratios and 95% confidence intervals (CIs) of breast cancer in relation to age at start of work at MMHL, position, and job status for women

Variables	Hazard Ratio	95% CI	p-value *
Age at start work (yrs)	1.07	0.97, 1.18	0.173
Position			
Technician	1.00		
Aid, clerk or ECG	0.67	0.08, 6.04	0.723
Job status			
Part time or causal	1.00		
Full time	1.45	0.14, 15.06	0.754

* p value from Cox proportional hazards model with age at start work as a continuous variable and position and job status as categorical variables.

Observed Cancer Cluster at MMHL

- **The hazard ratios from the Cox proportional hazard models were not statistically significant**
- **The occupational factor studied in this investigation (duration of time at work) was not associated with the increased incidence of breast cancer**
- **No specific exposures could be identified for studying potential association with the increase incidence of breast cancer in the employees at MMHL**

Field Investigations at MMHL

- **Walkthrough survey**
  - **Current chemical exposures are minimal due to use of sealed systems which minimizes handling**
  - **Volumes of chemicals handled are minimal**
  - **Exposures to physical agents such as heat, noise, radiation appear to be minimal**
  - **No significant exposures to ionizing radiation were apparent at the time of the survey; radioisotopes are seldom, if ever used, and IR sources are not present in the laboratory**

Field Investigations at MMHL (cont.)

- **Walkthrough survey**
  - **Past exposures to carcinogens was likely although the exposures levels are unknown, and therefore this can not be properly assessed.**
  - **Formaldehyde in formalin is a known carcinogen**
  - **O-toluidine, a rat mammary carcinogen, was a potential exposure in the past (sample preparation)**
  - **Poor indoor air quality may have lead to exposures to chemical carcinogens in the past (emissions from a hospital incinerator as well as roofing emissions were reported)**

Recommendations for further actions that emerged

- **Conduct a thorough chemical inventory and identify exposures to hazards compounds and use of any carcinogens and possible mammary carcinogens**
- **Conduct detailed exposures studies if hazardous chemical exposures are identified**
- **Ensure exposures to all forms of ionizing radiation are at background**
- **Provide information about risk factors for cancer to all MMHL employees**

Age, gender and duration of follow-up by disease status

- Since the March 2004 report, a new case of breast Ca was reported ; this brings the total number of cases to 11.With time, the denominator (time) has increased faster than numerator (Ca cases) and the SIR has decreased despite a new case.

Table. Observed and expected cases and age/calendar-year adjusted standardized incidence ratios (SIRs) for breast cancer (females only) and all cancers.

	Person years	Number of Subjects	Expected Cancers	Observed Cancers	Standard Incidence Ratio	95% Confidence Interval
Breast Cancer	**856.28**	**57**	**0.83**	**7**	**8.43**	**3.39-17.38**
All Cancers (Females only)	**856.28**	**57**	**2.18**	**10**	**4.59**	**2.20-8.44**
All Cancers (All Subjects)	**973.49**	**63**	**2.34**	**11**	**4.70**	**2.35-8.41**

Assessment of indoor air quality

- **No exterior air contaminant or exhaust discharges within 30 feet of the air intake.**
- **No interior air contaminant sources.**
- **Fan system filtration level – 85%**

Survey (Aug 2004)

- **CO2 – Assessment: good fresh air exchange**
- **CO – Assessment: good**
- **Relative Humidity – acceptable**
- **Temperature – Normal**
- **Supply duct clean; Exhaust duct – fine layer of duct**

Walk-through survey (Nov 2004)

Assessment of radiation exposure

- **Thermoluminescent dosimeters (TLD monitors) were exposed in the laboratory area for 70 days (June 18 – Aug 26).**
- **Typical natural background for the Fraser Valley during this period 0.12 mSv (milisieverts).**
- **Conclusion: Exposures measured at the MMHL area are typical natural background and the X-ray facility is not contributing to this natural background**
- **This natural background would not contribute measurably to increased cancer risk.**

Assessment of Carcinogenicity

- **US National Toxicology Program (NTP) has tested over 500 chemicals for risk of causing mammary tumors**
- **42 out of 500 were identifies as mammary carcinogens**
- **Four out of 42 are classified as human carcinogens:**

Benzene	Gasoline, solvent
1,3-Butadiene	Auto exhaust, rubber manufacture, gasoline
C,1 acid red 114	Dye for silk, jute, wool, leather
Ethylene oxide	Sterilizing gas for medical equipment

L.Bennett, B.Davis Environmental and Molecular Mutagenesis 2002

Assessment of Carcinogenicity (cont.)

- **Definitions:**

1. **Group 1: Agent (mixture) is carcinogenic to humans.**
2. **Group 2a: Agent (mixture) is probably carcinogenic to humans.**
3. **Group 2b: Agent (mixture) is possibly carcinogenic to humans.**
4. **Group 3: Agent (mixture) is not classifiable as to its carcinogenicity to humans.**
5. **Group 4: Agent (mixture) is probably not carcinogenic to humans.**

International Agency for Research on Cancer (IARC)

Assessment of Carcinogenicity (cont.)

- **Only one among 42 chemical substances known to have potential of causing mammary tumor was found: ETHYLENE OXIDE (Eth Ox) [Group 1].**
- **Concentration of Eth Ox was <0.1% => not reportable as hazardous product.**
- **27 substances that are used in MMHL were analyzed**
- **Based on the scientific knowledge none of the analyzed substances are present in a quantity or currently used in a manner that would result in an increased risk of cancer**

Walkthrough surveys on June 3; June 18 and July 23 2004.

Conclusions

- **The increased incidence of breast cancer in laboratory employees is an observed cluster.**
- **Using statistical analysis, we conclude that this increase is not related to age at start of work, job position, or job status**
- **On observation and literature review, no current occupational chemical exposures, or records of past occupational exposures were found that relate to breast cancer, or cancer in general**
- **No significant findings were found during radiation and carcinogenicity testing or on air quality testing**

Conclusions

- **The most likely explanation for the occurrence is a "chance cluster" or statistical anomaly**
- **It is recommended that this Cancer cluster investigation be closed. A new cluster investigation may be considered at future time for comparison (usually 5 years after the original investigation) using new cases and new data.**
- **Every effort should continue to be made, to ensure that the workplace remains as safe and free of carcinogens as possible.**

Questions welcome!

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Breast Cancer Occupational Risk Factors

- Band et al (2000) – population based Case-control study of 995 incident Breast CA (BCA) cases by menopausal status, controlling for Confounding factors
  - All F < 75 y.o with BCA diagnosed 1988 – 1989 (identified through BC cancer registry)
  - Controls randomly selected from 1989 BC Voter list
  - 1489 cases identified, 995 included into analysis
    - 318 (31.2%) premenopausal; 700 (68.8%) postmenopausal
    - Histol. confirmation obtained in all cases
    - Matched case-control analysis
    - Controlled for confounders (table)
    - 90% CI => 5% sign. (one sided)

Back

Breast Cancer Occupational Risk Factors

- Pre-menopausal: electronic data-processing, barbers, sales and material processing, food, clothing, chemical, transportation industries.
- Post-menopausal: health and nursing, school teaching, laundry/ dry-cleaning, aircraft/automobile incl. gasoline stations industries.

Back

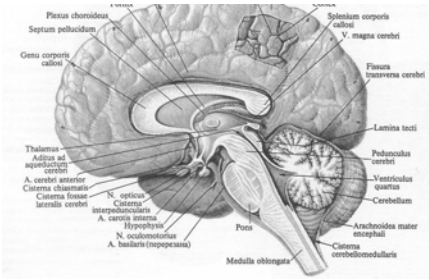
Band et al (2000)

Breast Cancer and rotating night shifts

Author	Year	Subjects	Findings	OR / CI
Tynes T, et al.	1996	2,619 Postmenopausal tele /radio operators exposed to nightshifts	F > 50 y.o. are at ↑ risk of BC	OR=4.3; 95%CI (0.7-26.0)
Pukkala E, et al	1995	Flight attendants (50 cases, 259 controls)	Lifestyle of F cabin attendants ↑ risk of BC	SIR=1.87; 95%CI (1.15-2.23)
Nabsen J.	2001	Matched case-control (7035 Danish F)	F who work @ night for at least 6 mo are at ↑ risk of BC	OR 1.5; 95%CI (1.2-1.7)
Davis S	2002	813 F cases (20-74) with BC; 793 controls	F exposed to LAT ↑ risk of BC	OR = 1.14 for each night per week; 95% CI (1.01 - 1.28)
Kliukiene J et al.	2001	15,412 Norwegian visually impaired women.	Blind F are at ↓ risk of BC	SIR = 0.51 (95% CI = 0.11-1.49).

Back

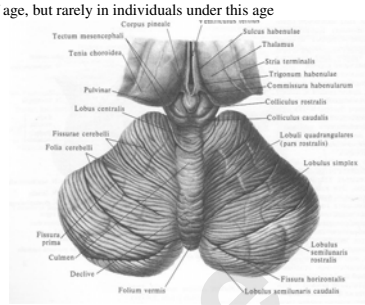
Pineal Gland



Back

Pineal body

The pineal body is variable in size and is calcified in 40% of subjects over 20 years of age, but rarely in individuals under this age



Back

Melatonin methabolism

- Melatonin is a hormone (N-acetyl-5 methoxytryptamine) produced especially at night in the pineal gland.
- Decreases with age, stimulates anti-oxidant action
- Its secretion is stimulated by the dark and inhibited by light.
- The suprachiasmatic nuclei (SCN) of the hypothalamus have melatonin receptors and melatonin may have a direct action on SCN to influence "circadian" rhythms.
- Melatonin is metabolised to 6-hydroxy-mel in the liver and the main metabolite excreted is 6-sulphatoxy-mel.
- Isolated measurements of mel are difficult to interpret given its circadian secretion, however urinary excretion of 6-sulphatoxy-mel may be helpful in studying pineal function especially in children.

Back

Melatonin as oncostatic in Breast Cancer

- Melatonin plays oncostatic role on hormone-dependent mammary tumors
  - Three antiestrogenic mechanisms:
    - acts through the estrogen receptor interfering with the effects of endogenous estrogens
    - Interfere with the synthesis of estrogens by inhibiting the enzymes controlling the interconversion from their androgenic precursors
    - decreases circulating levels of estradiol

Back

Sanchez-Barcelo E, et al. Melatonin-estrogen interactions in breast cancer. J Pineal Res. 2005 38(4):217-22.

Melatonin and night shifts

- 2004 Study by Eva S. Schernhammer et al:
  - Urinary measurements of 6-sulfatoxymelatonin over a 3-year period in 80 premenopausal women
  - assessed correlations between average urinary melatonin and plasma steroid hormone levels and evaluated potential associations between night work and hormone levels
  - significant inverse association between increasing number of nights worked within the 2 weeks preceding urine collection and urinary melatonin levels ($P = 0.008$)
  - significantly increased levels of estradiol after longer durations of night work (geometric mean levels of estradiol, 8.8 pg/mL for women who never worked night shifts versus 10.1 pg/mL for women who worked 15 or more years of night shifts; P for trend = 0.03).

Back

Schernhammer E S. et.al. Epidemiology of Urinary Melatonin in Women and Its Relation to Other Hormones and Night Work Cancer Epidemiology Biomarkers & Prevention Vol. 13, 936-943, 2004

Attachment 10

Laboratory Employees' Questions Arising from MMH Cancer Cluster Draft Report November 2005

November 9, 2005

QUESTIONS ARISING FROM MMH CANCER CLUSTER DRAFT REPORT

1] Clarification is required as to the comment that findings from previous Air quality studies were not available to investigators in the current process. Does this mean the findings are not archived or were they not provided by the employer?

2] As the report indicates exposures to smoke and odour were likely much higher in the past: a] what is the scientific opinion on the levels required [e.g. from dioxins or other byproducts of medical incineration] in order to make a causative link to the cancers identified?

b] Is it likely that the MMH smokestack produced these kinds of levels?

3] As recently as 2004 there are literature references as to the effects of burning medical waste [e.g. Chicago study]. Has such literature been canvassed in arriving at OHSAH's conclusions?

The members have asked for clarification as to the following:

4] What are the specific types of cancers classified at diagnosis? Do they suggest a common origin/agent?

5] How do these cancers compare to the 7 cancers now listed as occupational diseases for firefighters? Records indicate that MMH was exposed to toxic incinerator smoke twice a day for many years.

6] Is there any technical information about the fire detector system [particulate matter] which could explain the many "false" alarms over the years?
Did other organizations with similar systems have a similar experience with false alarms?

7] Would it be helpful to start up and run the incinerator and CSD ethylene oxide equipment, to monitor air intake of contaminants and get sample evidence for study?

8] Can hospital neighbours, as well as staff, provide anecdotal statements about the air quality issues at the time of the incineration?

9] What substance likely caused the corrosion of the Lab air intake vents?

10] Will FHA provide the sub-committee with the duct cleaning report?

11] Can OHSAH comment on the relationship between cancer causing agents and their probable impact on other systemic health issues, such as pregnancy?
12] What samples and tests are possible to detect toxic build-up in our bodies? [hair, nails, fat tissue etc.]? What type of Lab would do such work, and is FHA willing to participate in funding for this testing?

13] Can OHSAH please explain succinctly, what "stage" the investigation reached [1-4], and why no further stages are recommended?

14] Can we receive a set of monitoring recommendations specific to cancer cluster participants, as distinguished from the general population?

15] As similar labs apparently haven't reported cancer clusters, wouldn't this indicate a problem unique to MMH, vs just a statistical anomaly?

16] Will FHA provide gap funding for workers waiting for LTD or other benefits? Will FHA offer to address sick and vacation balances used to deal with cancer illness?

17] Will OHSAH make any more "suggestive statements" as to this being a suspicious work related cluster?

18] Will FHA lobby the WCB to cover these illnesses?

19] Will FHA provide compensation for employee's children who suffer birth defects?

20] Will the study be expanded to include all MMH employees, or can conclusions appropriately be extrapolated to cover all probable affected employees?

21] The time line chart will allow us to judge the accuracy of some of the plotted information, much has been undisclosed/lost previously due to confidentiality concerns. The Sept '05 summary statement noted 10 cancers/6 breast vs the April summary which said 11 cancers/7 breast? Is the Sept notation the correct one?

22] Does FHA have a plan to address non-Lab/non-RN staff, who may have potentially related illnesses?

23] Will OHSAH explain how the statistical monitoring of the original cancer cluster participants will be done? Why does the denominator need to be enlarged to include new employees, up to the next long term employee diagnosis date? Staff see this dilution as unnecessary. It's the long term employee group that seem to get diagnosed.

Attachment 11

OHSAH Response to Questions raised by Laboratory Employees January 2006

March 31, 2006

Mr. David Keen
Director Workplace Health
Fraser Health Authority

Mr. Marty Lovick
Senior Labour Relations Officer
HSABC

Dear David and Marty;

Enclosed please find a final version of the responses to the questions raised by the laboratory workers at MMH regarding the September 2005 Cancer Cluster Draft Report. This response document was drafted by Dr. Malcolm Steinberg, Ms. Tanya Tang, and me, and was reviewed by Dr. Annalee Yassi. It is included as a separate appendix to the Cancer Cluster Report (Attachment 11a). In order to ensure that this is not separated from the report, it is highlighted in the executive summary as a critical addendum.

We have responded to most of the questions conveyed to us in the November 9, 2005 letter, "Questions arising from MMH cancer cluster draft report". Responses to Questions 6, 8, 9, 10, 16, 18, 21(part), and 22 will be provided by FHA and included in this report as a separate doucument.

We have edited the Executive Summary to include details of the steps taken to enable feedback (directly or indirectly), to ensure the clarity and completeness of the report, and to emphasize that the approach taken in this work has followed international guidelines and practice. Finally, we hope that we have given a firm, but sensitively stated conclusion that this investigation is closed, at least with respect to OHSAH's current involvement.

Obviously this has been a difficult and emotional process for all people involved, not the least of which are the women and their families who were directly affected by this disease. We hope that this report will offer an opportunity for all persons involved to find closure.

Best Regards;

George Astrakianakis, PhD
Senior Occupational Hygienist

Cancer cluster study at Mission Memorial Hospital: A Response to questions by laboratory workers. March 31st, 2006

Questions and responses (to be included as a separate appendix):

1. *Clarification is required as to the comment that findings from previous air quality studies were not available to investigators in the current process. Does this mean the findings are not archived or were they not provided by the employer?**[Q.1]***[1]

Response: Based on a telephone conversation with the Mr. Quinn Danyluk, Occupational Hygienist with Fraser Health, the previous air quality surveys were simply standard surveys of 'indoor air quality' or IAQ. This included sampling for carbon monoxide, carbon dioxide, temperature and humidity, as well as verification of adequate ventilation. All results were unremarkable. The results of a recent IAQ survey (November 2004) are included as Attachment 5 in the report. More detailed environmental surveys were conducted including an assessment of radiation exposure (See Attachment 6) and a chemical assessment for carcinogens were conducted (See Attachment 7). Again, all results were unremarkable and did not identify any exposure source that might have contributed to increased cancer risk.

2. *As the report indicates exposures to smoke and odour were likely much higher in the past: A) what is the scientific opinion on then levels requires in order to make a causative link to the cancers identified? B) Is it likely that the MMH smokestack produced these kinds of levels? **[Q.2]***

Response: A) Any comments regarding levels required to make a causative link would be purely speculative without additional information. Among data we would need regarding the source emissions would be historical data on wind direction and velocity; atmospheric conditions (humidity, temperature, etc); as well as characteristics of the emissions, such as what was incinerated. However, decisions to pursue collecting these data would only be warranted if a conclusion were reached to proceed with further investigation. As discussed, this report recommends that this is not required. Moreover, it is not the levels of exposure that are of primary concern but which exposures occurred. B) At this stage we cannot comment on the nature of the emissions nor their levels without knowledge of what was incinerated and their quantity.

3. *As recently as 2004 there are literature references as to the effects of burning medical waste. Has such literature been canvassed in arriving at OHSAH's conclusions? **[Q.3]***

Response: The draft report (September, 2005) included a review of the literature from 1972 to 2005 with regards to the health effects of medical waste incineration. In addition to that, another two articles published in 2004 examined the reproductive health effects associated with solid waste incinerator operation.

[1] The bolded reference refers to the question number of the November, 2005 Questions from MMH Laboratory Employees document (See Attachment 10)

Tango *et al* (2004) investigated the association of adverse reproductive outcomes with maternal residential proximity to municipal solid waste incinerator in Japan. The study showed a peak-decline in risk with distance from the municipal solid waste incinerators for infant deaths and infant deaths with all congenital malformations combined. However, further investigation was suggested to accumulate good evidence for the reproductive health effects of waste incinerator exposure.[2]

Cordier *et al* (2004) assessed the impact of the solid waste incineration emission on birth defect rates at a region level of communities with fewer than 50,000 inhabitants surrounding 70 incinerators that operated at least one year in southeast France. The assessment found that the rate of congenital anomalies was not significantly higher in exposed compared with unexposed communities.[3]

4. *What are the specific types of cancer classified at diagnosis? Do they suggest a common origin/agent?* ***[Q.4]***

Response: Based on information available from the pathology reports, at their diagnoses of breast cancer, these women ranged in age from 38 to 67. Of these, 2 women had two tumours diagnosed each. One of these women was diagnosed with two primary tumours in the same breast at the same time; and one woman was diagnosed with one tumour in each breast with the diagnoses being two years apart. Taken as a group, there were 8 ductal-carcinomas and 1 lobular carcinoma diagnosed among 7 different women. In addition, I received the report of one woman who was diagnosed with ovarian cancer and one man who was diagnosed with skin cancer. I do not have the pathology reports for the remaining two women.

Both of the breast tumour types diagnosed, lobular and ductal carcinoma, are major sub-types of adenocarcinoma. At the time of diagnosis the pathologist may note adenocarcinoma if it is not possible to clearly identify which sub-type is present. Approximately 80% of breast cancer diagnoses are ductal carcinomas and 8% are lobular carcinomas. In the past, comedo-carcinoma was diagnosed separately; however, it is now recognized that this is a ductal carcinoma at an advanced stage. Comedo refers to the appearance of the tumour cell under the microscope.

Tumour cells from two women were found to be oestrogen receptor positive. Four of the tumours were found to be oestrogen receptor negative and the status for three of the tumours was not available from the pathology reports. Oestrogen receptor status is one indicator of potential treatment course. Tumours that are oestrogen receptor positive generally have a better prognosis and are likely to respond to hormonal manipulation.

[2] Tango T, Fujita T, et al. Risk of adverse reproductive outcomes associated with proximity to municipal solid waste incinerators with high doxin emission levels in Japan. J.Epidemiol. 2004;14 (3):83-93
[3] Cordier S, Chevrier C, et al. Risk of congenital anomalies in the vicinity of municipal solid waste incinerators. Occup Environ Med.2004;61(1):8-15

5. *How do these cancers compare to the 7 cancers now listed as occupational diseases for firefighters?* ***[Q.5]***

Response: There is no overlap with the cancer sites listed as occupational diseases for firefighters, which are: bladder, ureter, kidney, brain, colorectal, leukemia, non-Hodgkin's lymphoma.

6. *Can OHSAH comment on the relationship between cancer causing agents and their probable impact on other systemic health issues such as pregnancy?* ***[Q.11]***

Response: There are a number of cancer causing agents that are also mutagens such as radiation and diethyl stilbesterol (DES). In the case of radiation at sufficiently high doses exposure may cause cancer directly (Thyroid). At lower doses and during pregnancy itself, exposure may cause genetic defects among the offspring of exposed individuals. In the case of DES exposure is associated with increased risk of cervical cancer among the female children of exposed women who used this drug to decrease symptoms of morning sickness.

7. *What samples and tests are possible to detect toxic build-up in our bodies? What type of lab would do such work and is FH willing to participate in funding for this testing?* ***[Q.12]***

Response: There are many possible analyses for testing the presence of toxic exposures or their metabolites in the body. The choice of what sampling could be done will depend on whether one is searching for a marker of exposure, effect, or simply screening a population thought to be at risk. However, without a suspected target (eg. blood lead among battery manufacturing workers), individuals would be subjected to a number of invasive tests that likely would be of no benefit.

8. *Can OHSAH please explain succinctly what stage the investigation reached (1-4), and why no further stages are recommended?* ***[Q.13]***

Response: Based on the BC Cancer Agency and US-CDC guidelines, this study completed stage 2B. Since no potential cause has been identified, further evaluation is not suggested.

It is important to emphasize that, even if a potential etiologic cause had been identified, a large study sample would be required to demonstrate a statistically significant association between exposure and outcome if this indeed existed. The results of sample size calculations indicate a study that included at least 430 women (4:1 controls:cases or 344 controls and 86 cases) would have an 80% chance of identifying a two-fold risk (OR= 2.0) among a population where 50% of the women were exposed to the agent of interest. If the risk were lower (< 2) or the desired power greater (>80%), then the sample size would increase considerably.

Note: **Stage 1:** involves the gathering of basic information which include geographic, occupational, demographic, and some details regarding the individual cancer cases. Details regarding cancer cases are the most important facts. The outcome of this stage is either to move forward with a more detailed review, if the cancer cases prove to be similar diagnoses, or to conclude the investigation if a variety of different cancers are being suggested as the cluster.

Stage 2 is in two parts, a) case evaluation and b) incidence evaluation.

Stage 2a: please see the response to Question 4.

Stage 2b: involves the evaluation of the incidence of cancer, in this case breast cancer, among the group of subjects as compared to the provincial rates. The rates of incidence were indeed higher than expected with a calculated standardized incidence ratio (SIR) of 8.4; 95%CI (3.4-17.4) as was described in the Draft Report. What this number means is that the incidence of breast cancer among women identified as working in the lab at MMH is 8 times higher than the rate of breast cancer among women in the province of BC. Furthermore, we would expect that 19 times out of 20 (i.e. 95% CI) that the true ratio (since the above number is a statistical calculation) is between 3 and 17. The important point here is that the confidence limits do not include 1, meaning that the elevated ratio is 'statistically significant'.

The outcome from this stage is to move forward if the calculated incidence rate is elevated AND there is evidence to point to a common cause, or to stop if the calculated rate is not elevated. However, even if the rate is elevated, the decision to stop may be made if there is no evidence that would suggest a biologically plausible reason behind this cluster.

9. *Can we receive a set of monitoring recommendations specific to cancer cluster participants as distinguished from the general population?* ***[Q.14]***

Response: A fully-staffed occupational health unit, with occupational medical expertise as well as occupational health nursing staff, could organize mammograms for the workforce involved, so that results are provided confidentially not only to individuals, but pooled anonymous results are available to inform whether an occupational pattern of risk may exist. This is the recommended best practice in occupational health. However, it is more the custom in BC workplaces, where occupational health professionals (especially occupational medical physicians) are scarce, for individual workers to seek such screening on their own. Our publicly-funded health care system allows for this screening, and it provides individuals with privacy as well as confidentiality; also guaranteed in occupational health practice. However, when individuals seek screening related to workplace concerns on their own, it deprives the workplace from recognizing patterns of risk at early stages. In light on common practice in BC, it is probably more reasonable to suggest that women involved in this cluster consider consulting their family physician in order to seek guidance regarding mammograms and breast-self examination. Interpretation of test results in consideration of each woman's inherent risk factors (as highlighted in this report) can be provided by their family physician or through services offered by the BC Cancer Agency.

10. As similar labs haven't reported cancer cluster, wouldn't this indicate a problem unique to MMH versus a statistical anomaly? ***[Q.15]***

Response: Workforces generally do not know whether they are experiencing a cancer cluster unless there is considerable discussion amongst the workforce to alert themselves to this possibility and the investigation then undertaken. A cohort study has been initiated among health care workers affiliated with Vancouver Coastal Health in which the Health Sciences Association of BC has recently agreed to participate. This study my offer further clues regarding whether laboratory workers are at increased risk of breast cancer in BC as a result of what they are exposed to at work. However, at present there is no evidence in the scientific literature to suggest that any of the exposures encountered while working at the MMH are associated with increased risk of breast cancer, thus no comment can be made other than noting that it is indeed a statistically verified cluster of women who experienced a higher rate of cancer than would have been expected based on their age.

11. Will OHSAH make any more suggestive statements as to this being a suspicious work-related cluster? ***[Q.17]***

Response: The cluster is work-related only in that the women afflicted with this disease possessed a common job and a common place of employment. There is not sufficient evidence to support statements suggestive of work-related causation in the absence of evidence linking specific workplace exposures and breast cancer. Had the sample size been larger, a case-control analysis could have been conducted in which individual risk factors are reviewed in depth. The lack of an adequate sample size was cited by BCCA in their decision to not provide OHSAH with the individual level data we requested. It would not have been ethical or scientifically appropriate to approach any of the women diagnosed with breast cancer. If it was determined that there was sufficient justification to progress with the investigation beyond Stage 2B; only then, and in the context of an approved cohort or case-control study, would such detailed personal interviews be warranted.

12. Will the study be expanded to include all MMH employees or can conclusions appropriately be extrapolated to cover all probably affected employees? ***[Q.20]***

Response: Assuming the reference to affected employees refers to the Laboratory employees of MMH, the results of this cluster investigation are conclusive. We recommend that if there is reason to conduct a study of a larger population, such a study should be designed as a cohort study or case-control study, not an expansion of this cancer cluster investigation.

13. The September 2005 summary statement noted 10-cancers/6 breast versus the April summary statement which said 11 cancers/7 breast? Is the Sept. notation the correct one? ***[Q.21(partial)]***

Response: The report dated September 2005, includes a new case identified since the initial report (March 2004). The updated total is 11 diagnoses of cancer of which 7 were breast cancer cases among women.

14. Will OHSAH explain how the statistical monitoring of the original cancer cluster participants will be done? Why does the denominator need to be enlarged to include new employees up to the next long term employee diagnosis date? Staff sees this dilution as unnecessary. It's the long term employee group that seems to get diagnosed. ***[Q.23]***

Response: Incidence rates are calculated based on "years at risk". When rates are recalculated, because the study period has been expanded, person time will be added to the denominator and any new cases will also be added to the numerator. Dilution will occur only if this is a statistical cluster of breast cancer incidence and very few new cases are identified (See response to Q8). Further analyses can be incorporated to examine disease latency in order to investigate if timing of exposure plays a significant role in the determination of risk.

George Astrakianakis, PhD

With help from:
Dr. Malcolm Steinberg, MBBCh, DoH, MSc
Dr. Annalee Yassi, MD MSc
Ms. Tanya Tang, MSc

ABOUT THIS DOCUMENT

The Occupational Health and Safety Agency for Healthcare (OHSAH), which operated from 1998-2010, was a precursor to SWITCH BC. Conceived through the Public Sector Accord on Occupational Health and Safety as a response to high rates of workplace injury, illness, and time loss in the health sector, OHSAH was built on the values of bipartite collaboration, evidence-based decision making, and integrated approaches.

This archival research material was created by OHSAH, shared here as archival reference materials, to support ongoing research and development of best practices, and as a thanks to the organization's members who completed the work.

If you have any questions about the materials, please email hello@switchbc.ca or visit www.switchbc.ca