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Occupational Risk Identification for Ovarian Cancer

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Final Reports

Occupational Risk Identification for Ovarian Cancer

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BC Cancer Agency

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RS2003/04-002: Occupational Risk Identification for Ovarian Cancer

Final Report - 1-Year Renewal Grant

Background:
The purpose of this research is to identify potential carcinogens in the BC work environment for the ovarian cancer. Relatively little work has been done concerning occupational risk factors in ovarian cancer and suspected carcinogens have not been identified due to the lack of detailed exposure assessment at the individual levels. Mortality studies with BC women have shown elevated risks in teachers, nurses, and in hairdressers. Moreover, women at the present time constitute about one-half the BC workforce, and in the past 10 years have moved heavily into non-traditional jobs. For these reasons, women are potentially more exposed to occupational and industrial carcinogens than ever before. It is therefore important to examine the risks for ovarian cancer due to chemical exposure in the work environment more thoroughly so that preventive strategies can be established.

A case-control approach is used where cases (825) are ovarian cancer patients aged between 20 and 79; controls (825) are randomly selected from the general population, frequency matching on age distribution. A self-administered questionnaire approach is used. Participants are asked to fill out a questionnaire requesting relevant information. Individual exposure to occupational chemicals will be assessed by linking subjects' job histories and the job exposure matrices. The relationship between occupational exposures and the risk of ovarian cancer will be examined, taking into account other important confounding factors.

This 5-year research proposal was initially supported by a grant from the Workers' Compensation Board to collect research data for the first 2 years. The funding support has been subsequently renewed for one more year to continue the data collection. The plan was to collect 194 cases and 194 controls per year. Thus the planned workload would be to collect data from 1164 participants (582 cases and 582 controls). Due to unexpected legislation changes, we were unable to recruit controls as planned. A no-cost 9-month extension was requested and approved by the Board for continuing data collection for cases while waiting for a resolution to the control problem.

Progress:
The study is now at the end of the 1-year renewal grant. Overall although the research team has experienced some unexpected delays as described in previous reports, the originally planned workload has been essentially achieved with 1167 participants recruited (complete data collection for 1101 participants plus 66 more being followed-up). Due to the legislation changes limiting our ability to recruit controls, we have recruited more cases (n= 808) but less controls (n= 359). A solution for accessing the best source for the random selection of controls in BC (the Client Registry) has been approved by the Ministry of Health and we plan to use this approach to collect more controls in the next phase of this project as described below. We continue to do data clean-up including verifying the collected information and coding the occupational histories.

Future:
A grant proposal to collect more data and to conduct analysis has been developed and submitted to the Canadian Institutes of Health Research's 2007 competition.

RS2000/01-019: Occupational Risk Identification for Ovarian Cancer

A. Background

This is a 5-year study, aiming to identify potential carcinogens in the BC work environment for the ovarian cancer. A case-control approach is used where cases are ovarian cancer patients aged between 20 and 79; controls are randomly selected from the general population, frequency matching on age distribution. It is estimated that 825 cases and 825 controls will be recruited for the study. Exposure to occupational chemicals will be assessed by linking participants' job histories and the job exposure matrices (JEM). The relationship between occupational exposures and the risk of ovarian cancer will be examined, taking into account other important confounding factors. More information can be found in the complete research proposal (Appendix 1).

The study was funded by the Board for the first two years with primary focus on data collection. This final report summaries the progress of the study for this 2-year funding period. Additional funding for the study has been approved by the Board to continue data collection for another year starting December 1, 2004.

B. Progress

Overall the project has progressed very well although there was a delay at the beginning of the study. We have received good co-operation from the participants and the quality of data appears to be excellent in terms of completeness, particularly with work histories. We have also managed to incorporate all relevant comments from the external reviewers in the design and conduct of this study that undoubtedly have improved the scientific quality of the research. Individual aspects are described below.

1. **Unexpected Delay:** Originally the approved workplan was to recruit ovarian cancer patients diagnosed from September 1, 2001. Historically, the registration process of newly-diagnosed cancer cases to the Cancer Registry could take up to 6 months and this is a problem for studies of ovarian cancer as this disease can be rapidly fatal. In the first few months of the project we worked with the Registry to establish a rapid ascertainment process to reduce the delay time. A new process using electronic-scanning system has been successfully implemented where we are able to access newly-diagnosed ovarian cases within one to two months of their diagnoses. The development of this rapid ascertainment system unfortunately took longer than anticipated due to various reasons (eg. Christmas break, staff vacation and staff turnover, etc). Due to the delay, we began recruiting cancer cases diagnosed as of January 1, 2002 (not September 1, 2001 as originally proposed). We subsequently requested and received approval from the WCB Research Secretariat for a no-cost extension to complete the proposed work.
2. **Recruitment of participants:** A total of 693 women participated in the study with additional 222 women in the recruitment process. Most returned questionnaires have been thoroughly reviewed, supplemented with information from phone interviews, coded according to the Standard Canadian Occupational-Industrial Classifications, and entered into computer. On average, participants have about 5 jobs in her work history. The occupational information is virtually complete (less than 2% of jobs could not be classified). As expected, high proportions of women worked in traditional fields such as services (about 40% of the participants; among them 40 women worked as hairdresser), medicine (189 participants), although many also worked in agriculture (53), metal and other materials processing (52), fabricating and construction (47). Information provided on other factors is also virtually complete.

3. **Incorporation of reviewers' comments:** The research proposal was reviewed by 3 external reviewers who provided several thoughtful and constructive comments. Specific steps have been taken to incorporate the comments regarding the design and conduct of the study which can be briefly summarized as follows. Comments regarding the analysis phase will be incorporated in due course.

- We have added complementary expertise to the research team as suggested, including an epidemiologist with extensive experience in occupational hygiene (Prof. Paul Demers), a highly respected ovarian cancer medical oncologist (Dr. Kenneth Swenerton) and a molecular biologist specializing in population health research (Dr. Angela Brook-Wilson).
- Several components of the questionnaire have been substantially modified as suggested by the reviewers (new version attached in Appendix 2). The occupational questions have been revised to elicit for more details on tasks, percent of time at each task, average number of months worked and hours per week. These are particularly relevant for part-time jobs. The diet and medical background components have also been revised as suggested by the reviewers. We have also collected buccal swabs from participants (six per woman) for future studies.
- To improve exposure assessment, we will use the JEM currently being developed in our research group specifically for female workers in British Columbia (hereafter *Fem*JEM). At the first step, the development of the *Fem*JEM focuses on exposures with established relevance to ovarian and breast cancer including hair dyes, talc, asbestos, organic solvents, polycyclic aromatic hydrocarbons, ionizing radiation, electro-magnetic field and work-related physical activity. The approach developed in the Finnish Job Exposure Matrix has been used as an overall framework and as base-line assessments. The *Fem*JEM consists of estimates of the prevalence of exposure and the mean level of exposure among those exposed for each

occupation/agent/time-period combination. The overall framework specific to location of work as well as job tasks identified through the job descriptions has been established. Preliminary assessments will be modified to reflect the working conditions of BC women. The assessment will be also revised using information available from the JEMs previously developed in our research program for important industries in BC, actual measurement data from the BC Workers' Compensation Board (WCB) surveys, interviews with compliance officers from the WCB, and the NIOSH occupational hazards survey for the Northwest United States. Occupational hygienists with expertise in the industries of primary concern, as well as long term workers, will be identified for interview and consultation by our team members during the JEM development.

- We have taken a proactive approach in obtaining occupational information as well as other factors. Each returned questionnaire is reviewed by an industrial hygienist (Ms. Barb Lang who is also involved heavily in the development of the *Fem*JEM) to examine if the provided information is adequate for exposure assessment and by our project coordinator to identify information on other factors is complete. Participants are contacted by phone for clarification.
- The cases are population-based and all histologically confirmed. Although it might not be clearly stated in the proposal, the cases and controls are always selected using the same eligibility criteria to avoid potential biases; particularly women with history of previous cancers are excluded.

Appendix 1: The complete research proposal

INTRODUCTION and RATIONALE

In 1982, a comprehensive research program was initiated at the BC Cancer Agency, with overall aims of identifying occupational cancer risk factors[1-19] and potential carcinogens in the workplace.[20-26] The cancer incidence-based part of this program, which initially focussed on men,[15] has been expanded to include women with a first study investigating occupational risk factors associated with breast cancer.[17] As a further expansion, we propose a population-based case-control study of ovarian cancer to examine its relationship with occupationally-related chemical and physical exposures. The exposure to occupational substances will be estimated using the job exposure matrices (JEM) recently developed in our Occupational Oncology Research Program for major industries in British Columbia (BC) with supplemental information from the US Occupational Hazard Survey database (NIOSH JEM). A self-administered questionnaire approach will be used to collect relevant information on lifetime occupational histories, together with other important confounding factors. Occupational chemical exposures will be estimated by linking the lifetime job histories with the job exposure matrices.

Ovarian Cancer

Ovarian cancer is the fifth most common malignancy in BC women with an incidence rate of 16.1 per 100,000.[27] It is the most important cause of cancer death among the gynaecological malignancies. It is estimated that 353 new cases of ovarian cancer were diagnosed in 1999 in BC, [27] the majority (90%) being of epithelial origin. The incidence rate has remained stable over the past 10 years in both BC[27,28] and Canada.[29]

Workplace Exposures

Women at the present time constitute about half of the BC workforce, and in the past 10 years have moved heavily into non-traditional jobs. For these reasons women are potentially more exposed to occupational and industrial carcinogens than ever before. As more women choose careers which require delay of pregnancy and fewer children, significant interactions may also occur between exposure to workplace carcinogens and loss of the potentially protective effect of multiple births and early age at first birth for ovarian cancer. It is therefore important to identify occupational risk factors so that effective prevention strategies can be established. In contrast to the difficulties of implementing preventive measures in the general population for increased risks linked to lifestyle habits (eg. diet, smoking), such actions can effectively be taken for occupational risk factors. Once sufficient evidence for an association is obtained, modification of the industrial environment is usually technically feasible.

The Study

The proposed study will provide information on occupational risks for ovarian cancer based on lifetime exposures to chemical substances in the work environment. In this study personal exposure to occupational chemicals will be assessed at the individual-level using job exposure matrices. The odds ratios will be adjusted for known confounding factors, thus providing more precise estimates for the impact of occupational exposures on ovarian cancer risk. The study will also provide up-to-date information on risks associated with confounding factors.

PROJECT AIMS

The specific aims of the study are:

1) To identify workplace-related chemical and physical exposures associated with the risk of developing ovarian cancer, using detailed occupational histories and validated job exposure matrices

2) To evaluate parity, family history of cancer, duration of lactation, age at first birth, use of fertility drugs, tubal ligation, lifestyle factors, use of hair dyes, perineal powder exposure, physical activity, use of hormone replacement therapy, use of oral contraceptives and aspects of dietary intake as independent predictors of ovarian cancer risk, and as potential confounders in evaluation of occupational risk factors.

BACKGROUND

Occupational Risk Factors

Relatively little work has been done concerning occupational risk factors in ovarian cancer. Consequently little is known about risks of this cancer due to occupational exposures.[30] Although studies conducted in occupational settings have reported positive associations, their usefulness is generally limited by a lack of detailed chemical exposure data at the individual level and/or lack of information on important confounders. Proportional mortality studies (PMR) of BC women have shown elevated risks of ovarian cancer in teachers, nurses, and hairdressers.[2-11] A 1.5-fold excess mortality was observed for teachers and nurses. The excess risk, however, reduced to less than 20% when homemakers, accounting for approximately 91% of the female decedents,[3] were excluded from the analyses.[11] It has been suggested that the remaining professional women such as nurses and teachers may have lower parity and later age at first birth, along with a consequent increased risk of death from ovarian cancer. Absence of these protective lifestyle factors (high parity, early first birth) among teachers and nurses may account for the elevated risk. The current study will be able to evaluate whether this explanation is correct or whether these female professional groups are, in fact, exposed to occupational carcinogens. A recent US mortality study based on death certificates also found significant excess risks for teachers and nurses,[31] along with several other occupations and industries. Another mortality study of registered nurses indicated a similar positive association.[32] Confounding factors were not taken into consideration in any of the previous studies. Generally speaking, studies based on death certificates and record linkage suffer a major limitation in that little information on important factors such as parity, age at first birth and exogenous hormone use is available and hence direct adjustment is not feasible.

A two-fold mortality excess of ovarian cancer was observed for hairdressers in BC.[2] Notwithstanding common shortcomings of PMR studies and the limitations mentioned above, the observed excess may be due to exposure to hair dyes or other agents commonly used in this occupation. The excess cancer risk for hairdressers has also been reported by others.[33-36] A cohort study of over 11,000 American cosmetologists found a 34% elevated risk for ovarian cancer.[33] Another retrospective cohort study of over 7,000 Japanese female beauticians indicated similar levels of excess risk but this did not reach statistical significance.[34] A cohort

study of 29,279 hairdressers identified through the 1970 census in four Scandinavian countries, showed an overall mortality excess of 30% for ovarian cancer although the results were inconsistent from country to country.[35] A recent update study of Finnish women occupationally active in the 1970 census, supported the earlier findings for hairdressers.[36] In this update study, several substances were also identified as being associated with ovarian cancer. The authors linked the subjects' job titles with the comprehensive period-specific Finnish job-exposure matrix[37] and hypotheszed that the elevated risks were associated with several specific occupational exposures, including aromatic hydrocarbon solvents, leather dust, and man-made vitreous fibers.. It should be noted that these studies suffered the major limitation of not accounting for known confounders such as parity, family history of cancer, pregnancy related factors and exogenous hormone use. Another hospital-based case-control study suggests that the use of hair dyes may influence cancer risk[38] and a two-fold excess risk of developing ovarian cancer was observed for women dyeing their hair more than 5 times a year.

Several older mortality studies have found an association between ovarian cancer and long-term exposure to asbestos.[39-41] These were cohort studies of workers in textile and gas mask manufacturing industries where asbestos had been used. It has been argued that these cases might have been peritoneal mesotheliomas which incidentally involved the ovary; however since the studies were death-certificate based, no further information was available to investigate this possibility. A recent cohort study of women employed in two large printing plants in Moscow, Russia, found significantly elevated mortality from ovarian cancer among bookbinders, possibly due to the use of asbestos-contaminated talc fillers in paper.[42] Another cohort study of female pulp and paper workers in Norway reported an excess of ovarian cancer incidence.[43] Suspected occupational agents included talc, microbes, and different types of paper dust. Most important confounding factors were not adjusted for in these studies.

Elevated incidence of ovarian cancer has been observed among women exposed to ionizing radiation.[44-46] A mortality odds ratio study of women employed in the telephone industry found a two-fold excess risk.[47] The authors correctly cautioned that although exposure to new instruments introduced in modern telephone industry may account for the excess risk, confounding factors such as socio-economic status, parity and lifestyle, not incorporated in the study, may explain the observed associations.

A cohort mortality study of aerospace workers with detailed exposure assessment for trichloroethylene from a job-exposure matrix, has reported a 2.7-fold increased risk of ovarian cancer for women with medium or high levels of exposure.[48] Except for age and time period, the analysis was not adjusted for confounding factors.

A review of epidemiologic evidence on the relationship between pesticide exposure and cancer[49] has linked triazine herbicide use with ovarian cancer. Most studies examined however lacked detailed exposure assessment and the authors suggested that further studies with exposure assessment at the individual level be conducted to provide better information.

A case-control study of 229 ovarian cancer patients and the same number of population-based controls in China found a 2.7 fold elevated risk (with 95%CI of 0.6-13.9) for workers in the chemical processing and the rubber and plastic products industries.[50] Another hospital-based

case-control study with 296 ovarian cancer patients has reported a non-significant increased risk of developing ovarian cancer for those exposed to polycyclic aromatic hydrocarbons.[51] This study with detailed assessment also for talc, ionizing radiation, and solvents, found no excess risk associated with these chemicals. Although important confounding factors were adjusted, the small number of cases limited the power of these studies.

In summary, there is evidence of a relationship between occupational exposures and ovarian cancer. Most studies however suffered major limitations and a more detailed study is needed to clarify the risks. A recent review of 48 epidemiologic studies on occupational and environmental risk factors for ovarian cancer indicated that the evidence was characterized by poorly focussed data and was vulnerable to bias. The authors concluded that ovarian cancer is likely to have occupational relationships that inter-relate with lifestyle factors, and recommended that well-designed analytic epidemiologic studies be conducted to characterize occupational relationships reliably.[52]

Non-Occupational Confounding Factors

Although etiology of ovarian cancer remains largely unknown, several non-occupational factors have been identified as being related to its development. Reproductive-related factors have been implicated.[53] Differences in age at first birth[54] between ovarian cases and controls have been identified[55,56] and higher risks have been seen in women with no children or with low numbers of livebirths. High parity appears to reduce risk.[56] This relationship is observed across all age groups but seems to be strongest in younger women.[57] Studies have indicated a modest risk reduction associated with lactation.[58] The reduction was observed for short duration (6 months or less) of breast-feeding, and no further reduction was observed for longer duration.[59-60]

There appears to be an inverse association between use of oral contraceptives and risk of ovarian cancer after controlling for parity.[61-64] A strong and consistent decline in risk was seen with duration of oral contraceptive use up to 5 full years. No further decline in risk was seen in women using these preparations for 6+ years.[59]

Inconsistent results have been observed for hormone replacement therapy; some studies reported an increased risk[65,66] but other did not find an association.[67,68] The question of whether these factors alter the risk of developing ovarian cancer remains unanswered. An increased risk has been observed with the use of fertility drugs;[59,69] particularly an 11- fold increase for women using clomiphen (an ovulation-induction agent) for 12 or more menstrual cycles.[70] However a recent case-control study of Danish women did not confirm the excess risk for fertility treatment,[71] and the authors argued that the findings may not be due to treatment but to infertility itself.

Several studies have indicated that simple hysterectomy or hysterectomy with unilateral oophorectomy, is associated with higher risk of ovarian cancer.[72-74] Long-term reduced risk associated with simple hysterectomy has also been observed.[64,73-75] Lower risk of ovarian cancer for women who had undergone tubal ligation has been observed in several studies.[65,73-78] The reduced risk seems to be independent of other risk factors.[65] The protective effects of

hysterectomy and tubal sterilisation could be due to the reduction in hormonal activities resulted from these procedures.

Conflicting conclusions regarding the cancer risk associated with perineal powder exposure have been reported. Some studies have indicated an increased risk of ovarian cancer associated with perineal powder use;[76,79-81] however other studies did not observe such an association.[78,82-85]

A strong association between family history of cancer (breast, ovarian, endometrium) and the risk of ovarian cancer has been observed in several studies.[58,66,86] A further investigation using a large familial ovarian cancer registry indicated that patients from families with 3 or more ovarian cancer cases tend to develop their cancer at a younger age.[87] A recent meta-analysis reported a 3-fold increased risk to first degree relatives of those diagnosed with the disease.[88]

Diet and physical activity have also been linked to the development of ovarian cancer. A trend of increasing risk with increasing fat intake has been observed in 3 studies.[89-91] An increased risk was associated with higher intakes of cholesterol through frequent consumption of eggs and fried foods[91,92] has also been noted. No other consistent dietary finding have been seen for ovarian cancer, and consequently we have elected to restrict dietary information collected in this proposal to data on fat and cholesterol consumption. Although this will restrict our ability to address the effect of diet on risk it will allow insertion of risk estimates for the 2 major dietary components of concern into models to assess occupational exposures.

A recent population-based case-control study has found that women with high levels of leisure-time physical activity have a 27% reduction in risk of developing ovarian cancer, after adjustment for other factors.[93] It is hypothesized that the protective effect may be due to the alterations in metabolic pathways, for examples, reducing levels of insulin and insulin-like growth factors. No consistent relationship has been established between the risk of ovarian cancer and other lifestyle factors including smoking,[58,65,77] alcohol consumption,[68,77,89,92] and coffee consumption.[57,66,68,77]

Recent evidence indicates germline mutations in BRCA1 play a role in ovarian and breast cancer.[94-97] Analysis of chromosome data from 214 breast and ovarian cancer families found linkage at the BRCA1 locus in all breast cancer families with at least 1 member with ovarian cancer.[98] Cumulative risk of ovarian cancer in BRCA1 carriers was estimated to be 16% by age 50, and 63% by age 70 [99,100] and the overall risk for carriers of a BRCA2 mutation was estimated to be 27%.[101] BRCA1 germline mutations have been thought to account for a maximum of 10% of ovarian cancers,[102] however this original data come from a study of families with 4 or more cases of breast and ovarian cancer. Recent population-based data suggests that the figure is substantially lower, as the prevalence of such heavily affected families is, in fact, quite low.[97] It is estimated that the proportions of carriers in the general population and the ovarian cancer patients are approximately 0.12% and 3% respectively.[97,100]

Overall, although there has been a good deal of work done to elucidate hormonal and pregnancy factors in ovarian cancer, little is known to date concerning occupational risk factors. Given the current knowledge, it is clear that any study of occupational risk factors relating to ovarian cancer will have to take into account non-occupational factors. The proposed study will examine the occupational risk of ovarian cancer, with exposure data generated from detailed occupational

histories and job exposure matrices, while adjusting for important confounders. It will also provide good systematic data on non-occupational risk factors.

PRELIMINARY STUDIES

In 1982, a comprehensive occupational cancer research program was initiated at the BC Cancer Agency, with the overall aim of identifying occupational cancer risk factors and carcinogens in the workplace. Subsequently a methodic and stepwise epidemiologic research program was developed, consisting of inter-related and increasingly more specific studies ranging from broad-based hypothesis-generating investigations to cohort and case-control studies.[1-19] The investigators have participated in and/or directed many of these studies. The completed and on-going major studies include:

- an occupational mortality study, based on usual occupational, of more than 700,000 deaths (1950-1995) that examines the associations between occupation and both cancer and non-cancer causes of deaths
- a series of case-control studies involving 15,000 male cancer cases with complete lifetime occupational history and lifestyle information, in which the association between occupational exposures, characterized by job titles and industries, and the risks of developing cancer is examined
- A major case-control study of more than 1000 female breast cancer cases and 1000 controls, focusing on occupational history with complete assessment of hormonal and pregnancy-related factors
- a retrospective cohort study of over 4,000 aluminium reduction workers at the Soderberg process plant in Kitimat, BC, examining the relationships between occupational exposures in the BC aluminium industry and cancer mortality and incidence
- retrospective cohort studies of Canadian Airlines and Air Canada pilots, that examined occupationally related risks among airline pilots for both cancer and non-cancer causes
- a retrospective cohort study of over 30,000 pulp and paper workers, together with a nested case-control study, examining the relationships between occupational exposures and cancer mortality and incidence, using mill-specific Job Exposure Matrices
- development of job exposure matrices for main industries of BC, including pulp and paper, mining, agriculture and health care, in order to link these matrices to occupational databases for identifying carcinogens in the workplace.

The present study is part of the research program aiming to identify occupational risks for female workers. The BC Workers' Compensation Board has provided core funding for the research program since 1982. The funding covers the salaries of several core staff members, (including an occupational hygienist, programmer/statistician, an engineer, and a project co-ordinator) who provide support for the research program's field studies. Consequently the costs for several components of the current project are covered by the core funding and are therefore not requested. This funding arrangement has enabled the research program to keep a cadre of highly-trained, competent and experienced personnel on a long-term basis so that excellent support is available for field studies such as the present proposal.

RESEARCH DESIGN AND METHODS

Case Identification

Cancer cases will be identified through the BC Cancer Registry (BCCR) at the BC Cancer Agency. The BCCR is a population-based cancer registry which has been monitoring the occurrence of cancer in a defined population of approximately 4.1 million B.C. residents since 1969. Duplicate copies of pathology reports on newly diagnosed cancer cases are submitted to the Registry from every hospital and regional pathology service throughout the province. Accurate documentation on histology is available in at least 95% of all incident cases, and ascertainment for most sites is considered virtually complete. For cancer cases treated by the BC Cancer Agency's clinics (about 50% of all newly diagnosed patients), there is basically no delay in registration with the BCCR because of the on-line registration system. However for cancer cases not treated at the clinics, registration is done in two steps that could potentially cause a delay: (a) hospitals and regional pathology services send the reports to the Registry and (b) the registrations of these reports by the Registry. These two steps can take up to 6 months in some cases. Because ovarian cancer can be rapidly fatal (Table 1), we will activate a rapid ascertainment procedure with the registry whereby all pathology reports noting ovarian cancer will be copied upon reception and immediately sent to our study personnel. In addition, we will send letters describing our study to all members of the D.A. Boyes Society. This is an organization of gynecologists and other specialists throughout BC who treat gynecologic cancers. We will ask their co-operation in immediately reporting to our study coordinator all new cases of ovarian cancer seen during the data collection process. To ensure that cases are not approached twice we will use the computer software developed by our research group for tracking studies' participants to ensure newly identified subjects are automatically checked against the recruited subjects. We aim to recruit most of the cases within 3 months of their diagnoses. Notwithstanding the above rapid reporting arrangements, some 90% of ovarian cancer patients are seen at B.C. Cancer Agency clinics within 2 months of diagnosis for systemic therapy (chemotherapy) assessment. Thus rapid ascertainment and recruitment of cases in order to minimize losses to death should be feasible.

Cases eligible for study will be all women aged 20 to 79 years who are residents of British Columbia and diagnosed with ovarian cancer during a period July 1,2001 and December 31, 2006. Based on the number of cancer cases reported to the BCCR in 1997,[27] it is estimated that approximately 1,296 ovarian cancer cases age between 20 and 79 will occur during the case-ascertainment period. Of the 1,296 patients, about 117 (using lower limit of the 95%CI of survival proportion at 3 month in Table 1) will have died before being recruited leaving 1179 patients available for the study. Proxy respondents will not be included in the study. Although their inclusion would increase the number of participants, our experience[15-17] has been that information provided by proxies on occupational history may not be reliable.

Table 1: Survival rates for ovarian cancer (age 20-79), diagnosed between 1990-94 in British Columbia (n=1258 cases, BC Cancer Registry)

Month	Survival	Lower 95	Upper 95%
1	0.96	0.95	0.97
2	0.94	0.93	0.96
3	0.92	0.91	0.94

6	0.89	0.87	0.91
12	0.80	0.78	0.83

Control Identification

Controls will be selected from the general population through the Client Registry of the BC Ministry of Health. The registry covers approximately 99% of the B.C. population above age 20, including all subscribers of the BC Medical Services Plan. Recorded data include family name, given name, age, sex, mailing address, postal code and phone number. Female controls aged 20 to 79 will be randomly selected and frequency matched by 5 year age group to the subjects with ovarian cancer. Control names will be checked for prior history of cancer against the B.C. cancer registry. Controls with cancer history (except basal or squamous cell carcinoma of the skin) will not be eligible for this study. Controls who die before completing the questionnaire will be excluded and replaced by new ones from the same age groups. This is expected to be a rare occurrence. The Client Registry is sited in Victoria BC, Canada and has provided access to controls for several of our on-going and completed case-control studies such as the childhood leukemia study, [103] the testicular cancer study, [104] and the melanoma study. [105]

Data collection

All ovarian cancer patients, aged 20 and 79 years, ascertained by the BCCR during the study period will be invited to participate in the study. Their family physicians, identified on the pathology report, will be sent a letter explaining the study and asked whether it would be appropriate to contact the patients. In previous case-control studies, we have received extremely good co-operation from the medical community;[15-17] over 95% of the physicians approached gave approvals and in most cases refusals were due to patients' health status (death or too-ill to participate). In the previous case-control study of breast cancer, out of 1489 eligible cancer cases, physicians did not grant permission to contact for only 58 cases (3.9%).

Once permission is granted, patients will be sent a package containing a standardized etiologic questionnaire, an explanatory letter and a self-addressed stamped return envelope. The same questionnaire package will be mailed to control subjects.

The questionnaire will take approximately 50 minutes to complete and will cover the following areas.

i) Detailed lifetime employment history of all jobs held for 1-year or more including occupation and industry titles, duration and period of work. A job description is also requested in order to resolve ambiguities as to the actual work performed
ii) Detailed history for each pregnancy , including miscarriages and induced abortions.
iii) Detailed reproductive history, including age at menarche and menopause, use of fertility drugs, tubal ligation, history of hysterectomy with/out oophorectomy, oral contraceptive and postmenopausal hormone replacement therapy
iv) Detailed family history of cancer.

The following information will also be obtained:

Demographic characteristics, including date of birth, race, education, and marital status; medical history; family history of cancer; body height and weight; use of hair dyes and perineal powder usage, some aspects of diet; smoking and alcohol history; history of passive smoking in both residential and working environment; and physical activity level;. Although some ovarian

cancers are known to be associated with BRCA1 mutations, the proportion is small, and genetic testing would be prohibitively expensive. We have therefore elected to assess family history of cancer only—although if interesting findings appear, it may be possible to investigate genetic factors in future studies.

Returned questionnaires will be individually reviewed and subjects will be called to obtain missing information and to clarify ambiguous answers. For patients and control subjects who have not returned the completed questionnaire within two weeks, a reminder postcard will be sent. After this reminder, telephone calls will be used to follow up non-respondents at two-week intervals on three occasions. On each occasion three phone calls will be attempted at different times (morning, afternoon, and evening) to increase the chance of contact. Phone numbers and addresses of cases are generally very current; however for those who have moved, family physicians will be contacted for the information. The phone numbers and addresses of the controls who have moved will be obtained from the yearly updated B.C. telephone directories; and through access to the online database *Canada 411*. Failure to return the questionnaires after multiple prompting will be taken as evidence of a patient's refusal to participate in the study. Based on our experience from a recently completed case-control study of breast cancer the response rate is expected to be about 70% for both cases and controls.

Completed questionnaires will be coded and entered into a database for analysis. They will be reviewed manually and all data will be machine edited at the time of data entry. Before data entry, the front page of the questionnaire will be removed to ensure subject confidentiality. Occupations and industries will be coded according to the Canadian Standard Occupational Classification[106] (SOC-1980) and Standard Industrial Classification[107] (SIC-1980). This coding system will allow us to use the information from the US NIOSH JEM in exposure assessments. A translation of US occupational categories into Canadian classifications has been previously developed for this purpose[21] by our group. For occupations in major BC industries, locations of work and descriptions of tasks will also be coded according to the coding systems used in our BC-specific JEMs.

A draft questionnaire and the sample letters to physicians, cases and controls are provided in Appendix 1. The questions on occupations and industries have been used in our previous studies where we successfully coded virtually all of the occupational information on returned questionnaires. For example in a previous study,[15] out of 15,463 male participants who returned questionnaires, we were able to identify their longest held job for all but 109 men (0.7%). Similarly in the breast cancer study,[17] out of 2,033 female participants who returned questionnaires, we were able to identify usual occupation (longest held job) for all but 12 women (0.6%). The questions also provide adequate information for linkage with our JEMs. For example, the first 100 questionnaires from a case-control study[15] of men who had jobs in BC agriculture industry had a total of 221 BC agricultural jobs. Among them, 183 jobs (83%) were successfully linked using job titles, descriptions of tasks, time periods and locations of work; 31 jobs (14%) were in mixed farms and needed revised codes; 7 jobs (3%) were uncodable due to missing data.

Exposure Assessment:

The basis of the exposure assessment for individuals will be the JEMs previously developed in our research program for BC major industries including mining, lead and zinc smelter operations, pulp and paper and agriculture and other occupations. A health care JEM is currently being developed. Besides job titles and industries, the exposure assessments will be

specific to locations of work and types of task identified through the job descriptions. The agricultural JEM, for example, provides a retrospective description of BC farming practice since 1950. The matrix includes 45 commodities (crops or farming types) and nearly 300 chemical, biological and physical exposures in eight farming regions of BC.[26]
Assessments in the JEMs included level of exposure (concentration), duration of exposure (frequency), and/or opportunity for short-term high level exposures (peaks). The exposure levels were available either in qualitative (unexposed, low, medium and high) or quantitative forms. Of the 3000 assessments conducted in the agricultural JEM, 50% were assessed quantitatively.

For occupations not covered in our JEMs, the information from the occupational surveys conducted by the National Institute of Occupational Safety and Health (NIOSH) will be incoporated in the assessment.[108] The NIOSH JEM, kindly provided to us by Dr. Karl Sieber, was based on the original survey and included a cross section of American industries and occupational groups. Another national survey is currently planned by NIOSH (personal communication with Dr. Sieber). The proposed survey will take place in the next 2-3 years and will include the same industries as the original survey, but will follow a more comprehensive design. Preliminary discussion indicates that this would include ranking of exposure, frequency, magnitude and hazard potential. The updated JEM will be publicly available when complete. The timeline would fit nicely with our study and we will incorporate the improved estimates into our exposure assessments if possible to provide more precise estimates of cancer impact.

To ensure the data we use is as closely related to work practices in British Columbia as possible, we plan to initially concentrate on the NIOSH job titles from the Pacific Northwest Region. Because of the geographic proximity, this area has similar industries and climatic influence and is likely more comparable to BC than other regions, even those in Canada. Still, information extracted from the NIOSH survey relevant to our study will be reviewed by our occupational hygienist to ensure comparability.

Data Analyses

An initial descriptive analysis with frequency counts and ranges will be performed for all variables to isolate extreme values that require checking against the original questionnaire. Tabulations will be made of most data items to determine relative distributions of the cases and controls. Logistic regression and likelihood ratio test[109] will be used as the primary analytic tools. Statistical analyses will be carried out using SAS.[110]

Univariable analyses will be performed for all potential non-occupational risk factors. These include age, race; marital status; education (less than 12 years, high-school, vocational school, university, and professional school); body mass index (≤20, 21-25, >25: defined as weight in kilograms divided by height in meter squared); parity (0, 1-2, 3+); age at first birth (<25, ≥25); age at menarche (≤12, 12-15, >15); age at menopause; use of oral contraceptives including types and durations; hysterectomy (with and without oophorectomy); tubal ligation; use of fertility drug including types and durations; perineal powder exposure for various types and practices listed in the questionnaire and their durations of use; family history of cancer including first degree relatives, second degree female relatives; pregnancy history including number of pregnancies, number of full-term and incomplete pregnancies; smoking history with starting age, average number of cigarettes per days, total years smoked and number of pack-years; alcohol consumption with starting age, average number of bottles of beer, shots of spirits, glasses of wine per week, and total years of alcohol consumption; use of hair dyes including

starting age, duration, color groups; physical activity with various levels, frequencies and durations; and diet with individual items, saturated fat grouping, eating and cooking patterns.

Multi-variate analyses will be used to examine the relationships between important non-occupational factors and risk of developing ovarian cancer. That is, the effect of each risk factor is examined taking into account other non-occupational factors. Due to the large number of variables, the most parsimonious model for this examination will be identified using the forward selection process. Here the model is built by including the most statistically significant factor (say factor "a") and examining the remaining ones individually. The most significant one from this step (say factor "b") will then be added to the model (consisting of factors "a" and "b" at this stage) for examining the remaining ones. The process is repeated until no further significant factor is identified.

For occupationally-related exposures, multivariate analyses will be first performed for each chemical separately, adjusting for important non-occupational confounders via the parsimonious model identified above. Analyses to detect possible dose-response relationships will also be performed. For each of the chemicals with only qualitative assessments, an ordinal index will be created and assigned for individuals based on their exposed years at low, medium and high levels.

The cancer impact of exposure to multi-chemicals will be examined using two different approaches. The first approach is statistically based as described above where the most significant chemical will be included in the model and the remaining chemicals are individually examined to identify the next important one. The process continues until no other significant chemical is identified. The final model would provide the combination of chemicals that simultaneously affect the risk of developing ovarian cancer. Biologic and chemical information could then be used to generate hypotheses as to whether the chemicals act independently or synergystically.

The second approach is based on the specific structures of the chemicals. We have developed a coding system for substances based on their chemical and physical and biological properties.[20,25] The system provides a 10 digit code for each substance and is hierarchical in that each succeeding digit provides more specific structural data on the substances. For example, given the same first 7 digits, the last 3 digits coded as "11_" specify all compounds of chlorine, where "111" is for chlorates, "112" for chlorides and "113" for chlorites. Using this system, we will be able to examine the cancer impact of chemicals based on their specific structures from very specific, eg. chlorates, to more general, eg. chlorine compounds.

Overall, the resulting odds ratios should provide information on the cancer impact of occupational exposures, adjusting for non-occupational risk factors. Separate analyses will be performed for all cases together, and for epithelial cases only.

Study Numbers

Assuming a response rate of 70%, allowing for deaths and refusals, the total number of ovarian cancer patients available would be 825. The sample size of 825 cases and 825 controls matched by age frequencies, would allow detection of odds ratios for different prevalences of exposure (in the control population) given in Table 2. For a chemical exposure with a 10% prevalence, the detectable odds ratio would be 1.53 (representing 53% increase risk of developing ovarian cancer associated with this exposure) at 5% two-sided significance level and 80% power. The prevalence of occupations such as a teacher, nurse, clerical worker, and sale clerk was each greater than 10% based on lifetime job histories collected in our previous breast cancer study on occupational risk factors. There were 13% of controls who had never worked and were included in

the prevalence calculation. The prevalence of occupations such as electronic equipment operators, material (mine, metal, clay, glass, etc) processing workers, product fabricating workers, and personal services including hairdressers was about 5% individually. Although some chemicals are specific to particular occupations, there are others that may be prevalent in several occupations. The use of JEMs will allow for the assessment of exposure to specific chemicals across all occupations and hence increase the exposure prevalence rate and the power of the study. It is estimated that, based on these figures, the prevalence of exposure to specific chemicals could range from 5% to more than 20%, corresponding to a minimal detectable OR of 1.75 to 1.39 respectively. These prevalent rates will probably be higher in reality since over the last 10 years more women have entered the workforce and taken non-traditional jobs. Hence it is anticipated that the study would have adequate power to detect occupational risks although the power may be somewhat reduced in controlling for important confounding lifestyle and hormonal factors.

Table 2: Detectable odds ratios at 5% significance level (2-sided) and 80% power for 825 cases and 825 controls

Prevalence of Exposure (%)	Odds Ratios
5	1.75
10	1.53
15	1.44
20	1.39

RESEARCH TEAM

This research team has the expertise in epidemiology, exposure assessment, biostatistics, job exposure matrix developments, and occupational hygiene required for the interdisciplinary nature of this proposal. Specific details of the members' involvement are as follows.

- Nhu Le is a senior biostatistician with extensive experience in environmental and occupational epidemiology. He is the director of the BCCA occupational oncology research program. He has conducted/participated in several large-scale epidemiologic studies, particularly in the pulp and paper industry, along with population-based case-control studies for men and women. He will devote 20% of his time and be responsible for overseeing all aspects of the project. He will supervise the data collection process and statistical analysis.

- Joel Bert is a Professor of Chemical and Biological Engineering and an Associate Member of the Department of Pathology, both at the University of BC. He is a consulting scientist in the Cancer Control Research of the Cancer Agency of BC. He has been a key member of the occupational research program since its inception in 1982, involved in the developments of several job exposure matrices for important industries in BC. He will devote 5% of his time and be responsible for providing input to the exposure assessment component of the project.

- Richard P. Gallagher is a senior epidemiologist with extensive experience in occupational epidemiology, and studies of prostate cancer and skin melanoma. He is the head of Cancer Control Research at the BC Cancer Agency, and Clinical Professor in the Dept. of Health Care and Epidemiology at UBC. He has conducted/ participated in numerous large-scale epidemiologic studies. He has been a key member of the occupational research program

since its inception in 1982. He will devote 5% of his time and be responsible for providing epidemiological input to the project.

- Barbara Lang is an occupational hygienist with experience in the development of job exposure matrices as well as in assessing exposures in industry (lead/zinc smelter). She will devote 10% of her time to participate in the exposure assessment.

All members of the principal investigation team will participate in the dissemination of the results through scientific conferences and peer-reviewed publications.

FUTURE PLANS

This study focuses on the risks of ovarian cancer due to occupational exposures-characterized by linking the job exposure matrices to job titles/industries. The findings will identify potential carcinogens in the workplace and provide additional information on ovarian cancer risk for non-occupational risk factors.
As noted earlier, the effects of BRCA1 and BRCA2 mutations are not examined in the current proposal. The low prevalence in the general population dictates that they should be examined in more specific subgroups.

This study may serve as a basis for a further study aimed at identifying women with a strong family history of breast and ovarian cancer. A "family history positive" proband will be defines as a women with any first or second degree relative with ovarian cancer, early (before age 50) breast cancer or male breast cancer. All family history positive women and a sample of family history negative women can then be recontacted and asked to participate along with selected relatives in a genetic epidemiology study. This investigation would require blood samples and would be aimed at identifying women who are carriers of BRCA1 and 2 mutations. The objective would be to investigate gene-environment interactions in ovarian cancer. Because of the small numbers of women who will be BRCA1 positive in our study, the principal investigation team are seeking to collaborate with other investigators in the United States and Canada to investigate the population-based genetic aspects of ovarian cancer. This aspect of the study will be developed separately.

Confidentiality

Only persons directly involved in the study will have access to data identifying individual subjects. Records and forms will be kept in locked file cabinets when not in use. Names of subjects are obtained for record-keeping purposes only. No name data will be kept on questionnaires returned by subjects as all individual participants will be allocated a study number. The computerized record linking name to study number will be maintained under specific file name with password protection in the Cancer Control Research Unit. No individuals will be identified by name in any published results of the study.

Ethics

Prior to the start of this study ethical approvals will be in place from the Behavioural Research Ethics Committee, University of British Columbia (UBC) and the Clinical Investigations Committee, BC Cancer Agency (BCCA).

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Appendix 2: Questionnaire

Hard copy of questionnaire can be found in original file.

RS2003/04-002: Occupational Risk Identification for Ovarian Cancer

Final Report
(1-Year Renewal Grant)

Background:
The purpose of this research is to identify potential carcinogens in the BC work environment for the ovarian cancer. Relatively little work has been done concerning occupational risk factors in ovarian cancer and suspected carcinogens have not been identified due to the lack of detailed exposure assessment at the individual levels. Mortality studies with BC women have shown elevated risks in teachers, nurses, and in hairdressers. Moreover, women at the present time constitute about one-half the BC workforce, and in the past 10 years have moved heavily into non-traditional jobs. For these reasons, women are potentially more exposed to occupational and industrial carcinogens than ever before. It is therefore important to examine the risks for ovarian cancer due to chemical exposure in the work environment more thoroughly so that preventive strategies can be established.

A case-control approach is used where cases (825) are ovarian cancer patients aged between 20 and 79; controls (825) are randomly selected from the general population, frequency matching on age distribution. A self-administered questionnaire approach is used. Participants are asked to fill out a questionnaire requesting relevant information. Individual exposure to occupational chemicals will be assessed by linking subjects' job histories and the job exposure matrices. The relationship between occupational exposures and the risk of ovarian cancer will be examined, taking into account other important confounding factors.

This 5-year research proposal was initially supported by a grant from the Workers' Compensation Board to collect research data for the first 2 years. The funding support has been subsequently renewed for one more year to continue the data collection. The plan was to collect 194 cases and 194 controls per year. Thus the planned workload would be to collect data from 1164 participants (582 cases and 582 controls). Due to unexpected legislation changes, we were unable to recruit controls as planned. A no-cost 9-month extension was requested and approved by the Board for continuing data collection for cases while waiting for a resolution to the control problem.

Progress:
The study is now at the end of the 1-year renewal grant. Overall although the research team has experienced some unexpected delays as described in previous reports, the originally planned workload has been essentially achieved with 1167 participants recruited (complete data collection for 1101 participants plus 66 more being followed-up). Due to the legislation changes limiting our ability to recruit controls, we have recruited more cases (n= 808) but less controls (n= 359). A solution for accessing the best source for the random selection of controls in BC (the Client Registry) has been approved by the Ministry of Health and we plan to use this approach to collect more controls in the next phase of this project as described below. We continue to do data clean-up including verifying the collected information and coding the occupational histories.

Future:
A grant proposal to collect more data and to conduct analysis has been developed and submitted to the Canadian Institutes of Health Research's 2007 competition.

Additional copies of this publication may be obtained by contacting:

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