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UTILITY OF DEATH CERTIFICATE DATA IN PREDICTING CANCER INCIDENCE

by

Ronald L. Bedford

A thesis submitted in partial fulfillment
of the requirements for the Master of
Science degree in Occupational and Environmental Health
in the Graduate College of
The University of Iowa

December 2009

Thesis Supervisor: Professor R. William Field

Graduate College
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Iowa City, Iowa

CERTIFICATE OF APPROVAL

MASTER'S THESIS

This is to certify that the Master's thesis of

Ronald L. Bedford

has been approved by the Examining Committee
for the thesis requirement for the Master of Science
degree in Occupational and Environmental Health at the December 2009
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To Frances Roushar, my wife, and Bill Field, my mentor, both of whom believed in me

ACKNOWLEDGMENTS

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INTRODUCTION

Retrospective cohort mortality studies rely heavily on information provided by the National Center for Health Statistics' (NCHS) National Death Index (NDI) for mortality ascertainment activities. Since the NDI's computerized index of death records with codes identifying cause of death (COD), NDI *Plus*, only includes records dating back to 1979, ascertainment of accurate COD data before that date is much more problematic in retrospective cohort mortality studies that include a sizable worker population predating the NDI. In order to assess COD in workers prior to the NDI, both the collection and International Classification of Diseases (ICD) coding of death certificates (DCs) is required for each decedent.

Occupationally-related cancer epidemiology also relies on mortality reporting; however, cancer incidence information provides a more complete picture of the overall disease burden. Rather than merely identifying what may have caused a subject's death, incidence data describe what cancers may have been affecting that worker at the time. This additional information allows a more complete assessment of potential workplace hazards and their effects on workers. In the U.S., the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program along with the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) collect information about cancer occurrence and mortality for the entire population. Unfortunately, many of these registries have only recently been established or fully supported (National Program of Cancer Registries [NPCR], 2008)

The overall objective of this research is to assess the ability of DCs to reflect cancer incidence within a population of decedents. We hypothesize that information

provided by DCs will under-report cancer incidence identified by the Iowa Cancer Registry (ICR) from its inception on January 01, 1973 through December 31, 2005. We also hypothesize that the ability of the DC to reflect cancer occurrence is directly related to the survival time after cancer diagnosis. A third hypothesis is that factors such as age at diagnosis, ICD revision in use at time of death, diagnosis era, race, and gender may be related to the reporting of cancer occurrence on DCs. A greater understanding of how well cancer incidence can be predicted from DCs is a priority need in the current Department of Defense (DoD) funded Iowa Army Ammunition Plant (IAAAP) Munitions Workers Study, as well as other retrospective studies whose workers are located in areas that have only recently been covered by population-based cancer registries. The hypotheses will be explored in the following three **Specific Aims** by comparing CODs that appear in DCs with cancer incidence data from the ICR for IAAAP cohort members.

SPECIFIC AIMS

Specific Aim I

Determine the agreement between cancer occurrences reported on DCs versus cancer incidence recorded by the ICR for the study population.

Sub Aim 1

Determine the agreement between cancer occurrences listed as the underlying cause of death (UCOD) on DCs versus cancer incidence recorded by the ICR for the study population.

Sub Aim 2

Determine the agreement between cancer occurrences listed among all conditions coded (ACC) on DCs versus cancer incidence recorded by the ICR for the study population.

Specific Aim II

Determine whether survival time after cancer diagnosis affects the agreement between cancer occurrences reported on DCs versus cancer incidence recorded by the ICR for the study population.

Sub Aim 1

Determine whether survival time after cancer diagnosis affects the agreement between cancer occurrences listed as the UCOD on DCs versus cancer incidence recorded by the ICR for the study population.

Sub Aim 2

Determine whether survival time after cancer diagnosis affects the agreement between cancer occurrences listed among ACC on DCs versus cancer incidence recorded by the ICR for the study population.

Specific Aim III

Determine whether other factors including age at diagnosis, ICD revision in use at time of death, diagnosis era, race, and gender affect the agreement between cancer occurrences reported on DCs versus cancer incidence recorded by the ICR for the study population.

Sub Aim 1

Determine whether other factors including age at diagnosis, ICD revision in use at time of death, diagnosis era, race, and gender affect the agreement between cancer occurrences listed as the UCOD on DCs versus cancer incidence recorded by the ICR for the study population.

Sub Aim 2

Determine whether other factors including age at diagnosis, ICD revision in use at time of death, diagnosis era, race, and gender affect the agreement between cancer occurrences listed among ACC on DCs versus cancer incidence recorded by the ICR for the study population.

BACKGROUND AND SIGNIFICANCE

The NDI greatly facilitates both the accurate and complete ascertainment of vital status (VS) and COD information for use in epidemiologic studies. Operating within the CDC's NCHS, the NDI is a repository of electronic death record information provided by State vital records offices dating back to January 1, 1979. Unfortunately, because NDI records only go back to 1979, determination of COD prior to the NDI's inception is more problematic in retrospective mortality studies that include a significant population of workers from the pre-NDI era. To ascertain cancer-related CODs for workers that predate the NDI, both the collection and ICD coding of the DC is required for each decedent.

Thirty years ago, Frazier and Wegman (1979) stressed the need for additional studies to evaluate the use of DCs as part of an occupational health surveillance system. However, since that time, few researchers have examined the utility of DCs in occupational epidemiology studies. Dubrow, Sestito, Lalich, Burnett, and Salg (1987) indicated that the use of DCs is a cost-effective and simple approach to the preliminary investigation of occupational disease surveillance. Burnett and Dosemeci (1994) pointed out that the strengths of DCs stem from their wide spread use, while the limitations include lack of accuracy and incomplete data.

This research is intended to provide insights into how well selected invasive cancer occurrences can be ascertained solely from DCs. Information regarding the ability of DCs to "detect" certain cancers is a priority need in the current, University of Iowa based, DoD-funded IAAAP Munitions Workers Study, as well as other retrospective DoD and Department of Energy (DOE) studies of workers that predate the establishment

of population-based cancer registries. The information provided by this evaluation will help guide our interpretation of the cancer-related data used in the National Institute for Occupational Safety and Health (NIOSH) Life Table Analysis System (LTAS.). For example, can we expect to detect certain cancers with long survival periods in the cohort of IAAAP workers by relying solely on DC information?

LITERATURE REVIEW

Introduction

Our review of the literature found very few studies that examine the utility of DC information to assess cancer incidence. In a retrospective occupational cohort study, Demers et al. (1992) examined cancer identification by DCs compared to a tumor registry. Using data from concurrent incidence and mortality studies, the authors reported "The observed relative risk estimates for rapidly fatal cancers were similar using the two sources of information, and no increase in precision was observed."

Percy, Stanek, and Gloeckler (1981) and Percy, Miller, and Gloeckler Ries (1990b) reported on the accuracy of cancer reporting on DCs in two separate, but similar studies. In the earlier study, using data on cancer deaths occurring during 1970 and 1971, the authors used information on both incident and prevalent cancers from the National Cancer Institute's (NCI) Third National Cancer Survey (TNCS.) The more recent investigation focused on incidence data for cancers diagnosed during 1974 and 1975 and followed to death through 1986 as well as cancers identified by DCs during 1985 and 1986 that were confirmed in a SEER area between 1973 and 1986. Examining agreement between DCs and cancers reported by the registries, both studies calculated percent agreement between cancers reported on DC and confirmed by the registry compared to cancers identified by each source separately. Overall agreement was good with approximately two-thirds of cancers falling into the category deemed reliable by the authors. Both studies also found discrepancies in validity for various cancer sites and noted both over and under-reporting.

Cause of Death Reporting Compared to Autopsy Findings

The inaccuracy of COD reporting is a recognized shortcoming of DCs when used for medical surveillance. Several studies have compared DCs to various diagnostic criteria. While autopsy is generally considered to be among the most precise diagnostic tools available, there has been a lack of consensus about the accuracy of DC reporting compared to post-mortem examination. In a yearlong population-based study involving necropsy of 96.5% of all decedents in an East German municipality, Modelmog, Rahlenbeck, and Trichopoulos (1992) reported a difference between the COD reported on DC and autopsy findings in 47% of cases. However, the researchers noted that the deaths attributed to cancer on the DC showed relatively high, though still unsatisfactory, sensitivity, and predictive values.

In another study that compared the accuracy of DC-reported COD to autopsy findings, Schottenfeld, Eaton, Sommers, Alonso, and Wilkinson (1982) found that 15% of DCs needed to have the underlying cause of death (UCOD) recoded and another 11% had discrepancies that did not require recoding. The authors reported that among the two most common categories of underlying cause, neoplasms and vascular diseases, there was a 95% agreement between DCs and autopsy. While neither of these studies is conclusive with regard to use of DCs for cancer surveillance, both support a relatively high degree of accuracy associated with cancer diagnoses on DCs.

Several authors have examined COD reporting with respect to cancer specifically. Hoel, Ron, Carter, and Mabuchi (1993) found considerable variability in the rate of errors on DCs related to type of cancer, age at death, and time period. Engel, Strauchen, Chiazze, and Heid (1980) suggested that autopsy results may not have been utilized to

their fullest extent in filling out the COD on DCs. The authors reported incorrect UCOD on 42% of DCs for autopsied subjects, with cancer under-reported by approximately 10%. In approximately 89% of cases, the UCOD listed on the DC was confirmed, by autopsy, as having existed without regard to its role in the sequence of events leading to the death of the subject.

Cancer-Related COD on DC Compared to Registry Data

CODs attributed to cancer on DCs have also been compared to reporting by cancer registries. In addition to the studies by Demers et al. (1992) and Percy et al. (1981; 1990b), Freedman, Sigurdson, Doody, Love-Schnur, and Linet (2006) reported 35% under-ascertainment of cancers identified by DCs compared to registry data among radiologic technologists in the United States (U.S.). Several studies have also examined the accuracy of DC-reporting of specific types of cancers. As may be expected, the results from these studies are mixed. Chow and Devesa (1996) reported that cancer diagnoses reported on DCs showed good accuracy when compared to diagnoses reported to the SEER program. Cottrell, Schwartz, Sokas, Kofie, and Welch (1992) and Davis, Martin, and Kligler (1992) examined mesothelioma surveillance using DCs in the setting of a District of Columbia occupational mortality study and for general disease surveillance in Massachusetts and reported poor ascertainment using only the UCOD. However, the authors reported better agreement when DCs were reviewed manually for any mention of the disease of interest.

In a recent article assessing the accuracy of COD reporting for subjects in a prostate cancer screening trial in Finland, Mäkinen et al. (2008) reported overall agreement, sensitivity, and specificity all greater than 96% when comparing the COD

reported on DCs to determinations of the COD based on medical records by a six-member panel of expert reviewers. In addition, Rushton and Romaniuk (1997), in their study of leukemia among an occupational cohort of U.K. petroleum workers, reported that "for the majority, the diagnosis on the death certificate was more specific than that on the cancer registration." However, because of differences in surveillance methods outside the U.S., the findings of studies performed elsewhere may be less generalizable to the U.S.

Mortality Data and Cancer Identification

Using cancer mortality figures to reflect cancer occurrence has been widely criticized, but a lack of agreement about the extent of the limitations of mortality data for cancer surveillance persists. According to Boyle (1989), incidence data may be affected by biases due to misdiagnosis and under-ascertainment, but the author considers these to be less significant than the problems associated with mortality data, which include the same shortcomings plus other compounding factors. Feinstein and Esdaile (1987) recommended eliminating use of cause-specific mortality rates due to the inaccuracy of DC-reported COD and development of a separate DC with information intended for scientific purposes. The authors concluded that the death certificates available in 1987 "cannot be used as scientific instruments for denoting diseases or indicating lethal maladies." On the other hand, in his review of uses of mortality data for cancer surveillance, Griffith (1976) reported that DCs are accurate and specific enough to show major differences and trends.

Despite disagreement about the accuracy of the data provided, DCs continue to be relied upon for cancer reporting. In a study of cancer incidence among radiologic

technologists during 1983 to 1998, Sigurdson et al. (2003) reported that 29.4% of all cancers included in the study were identified by DCs and the CDC's NDI *Plus*, which relies on COD reporting from state departments of vital records. The authors relied on mailed questionnaires for the remainder of their cancer incidence ascertainment and were able to validate 74% of reported cases with medical records. Limitations of this study may include the use of DC-only (DCO) cancer identification and the fact that death records and self-reporting were the only means of cancer identification available.

For almost 50 years, the American Cancer Society (ACS) has used DC data as part of its formula for estimating cancer incidence, and periodic reviews have deemed the results useful and reliable (Silverberg & Lubera 1983). Describing the new method of estimating cancer incidence adopted by ACS, Pickle et al. (2007) criticized the use of mortality information for its weak link to incidence in cancers with better survival rates.

RESEARCH DESIGN

Background

Iowa Army Ammunition Plant Study Overview

Under contract to the Department of Defense (DoD), researchers at the University of Iowa's College of Public Health are conducting a study titled: *Epidemiologic Health Survey of Department of Defense Contract Workers at the Iowa Army Ammunition Plant in Middletown, IA: Analyses of Cohort Mortality/Cancer Incidence and Surveillance for the Prevalence of Positive Beryllium Lymphocyte Proliferation Tests* to examine the health of current and former workers at the Iowa Army Ammunition Plant (IAAAP) near Burlington, Iowa. The broad objective of the IAAAP project is to examine the mortality experience for a cohort of workers employed at the IAAAP with a sub-study examining the cancer incidence for a restricted population (Iowa residents) within the cohort. A subset of the cohort will also be assessed for the prevalence of a positive response to beryllium lymphocyte proliferation tests (BeLPT). The IAAAP researchers hypothesize that there may be increases in mortality, cancer incidence, or beryllium sensitization (BeS) for the DoD contract workers currently or previously employed at the IAAAP. The rationale for the proposed research is that the workforce is known to have engaged in work processes that involve the use of carcinogens and others toxicants, in some cases, before it was clearly known whether the substances had the potential to cause adverse health outcomes (Field & Fuortes, 2005).

The IAAAP study will evaluate the work-related health experience of approximately 37,000 workers employed at the plant during the period January 1, 1951 to December 31, 2005. The employee cohort was assembled from personnel records

consisting of index cards and two sets of computer files provided by the firm contracted to provide labor services for the IAAAP. Name, Social Security Number (SSN), job codes, and dates of hire and termination were included for the majority of the personnel records for the workforce. Job descriptions and exposure data were compiled by professional industrial hygienists. Personal identifiers (name and SSN) from plant records were examined and cross-checked for duplication, original typographical errors, or data entry errors.

Identification of VS and COD

The IAAAP cohort data set were matched against data from the Social Security Administration (SSA) to verify identity, verify linkage with the plant's employer identification numbers, and determine VS. COD information was requested from NDI *Plus* for cohort members identified as deceased since 01/01/1979. For earlier deaths or workers not matched by the NDI, the DC or equivalent information was requested from the vital records bureau in the state identified as the former employee's state of last residence or benefit.

Identification of VS and CODs within Iowa

The availability of the IAAAP study mortality data and the accessibility of ICR cancer incidence data provided a unique opportunity to assess the ability of DCs to reflect invasive cancer incidence within a population of decedents. The ICR has access to DC information dating back to 1973, in the form of an annual mortality database provided by the Iowa Department of Public Health (IDPH.) The mortality database includes information recorded on the DC by the certifier (physician or medical examiner/coroner) in the same format reported to the NDI for deaths that occurred since 1979. COD

information was coded by a nosologist at IDPH to the ICD revision in use at the time of death. To identify decedents in Iowa, the IAAAP cohort data were matched against VS and COD information from the IDPH mortality database. As in other states, DCs were requested from the IDPH for deaths that occurred before 1973 and for workers not matched by the ICR database.

Study Design

This study uses a retrospective cohort design to examine the relationship between DC-reported COD information and cancer incidence among a subset of contract workers at an Army ammunition plant between 1951 and 2005. DC information for the study was assembled from the mortality database provided to the ICR by the IDPH. Cancer incidence data for the study were provided by the ICR. The IAAAP Study received human subject approval from the University of Iowa's Institutional Review Board. This research is considered part of the DoD project and involved no additional collection of data outside what was ascertained for the overall DoD project.

Subject Selection and Source Population

The eligible cohort was defined as IAAAP Munitions Workers Study subjects whose deaths were certified by the IDPH as having occurred in Iowa between January 01, 1973 and December 31, 2005 and who were identified by the ICR with a first incident primary malignant neoplasm during the same period.

Decedents in Iowa were identified by matching the IAAAP cohort dataset against VS and COD information from the IDPH mortality database. The IAAAP cohort data were also matched against ICR records, which will be the sole source for identifying

incident cancer cases. The study timeframe will allow evaluation of cancer incidence from the inception of the ICR in 1973 to 2005.

Subject Inclusion Criteria

Study subjects met the following inclusion criteria: 1) employment at the IAAAP for at least one day between 01/01/1941 and December 31, 2005; 2) registered by the ICR with a first primary malignant neoplasm between January 01, 1973 and December 31, 2005; and 3) confirmation of death by the IDPH between January 01, 1973 and December 31, 2005. Both male and female former workers of any age were included.

Matching Criteria

A hierarchical matching algorithm was established with assistance from the IAAAP study database manager and ICR data management staff. The matching criteria were conservative, relying on a nine digit SSN match and full or weighted partial name match between plant records, the IDPH mortality database, and ICR cancer incidence records. All potential subjects with less than a complete name match were examined to assure, to the extent possible, the validity of the match. Since many of the original plant records predate electronic media, apparent typographic errors were not uncommon. Minor spelling discrepancies and first and middle name transpositions were accepted. Matching of female cohort members presents an increased challenge for the matching system because of last name variations associated with changes of marital status. Female cohort members were included if both their SSN and first name on the DC matched the verified plant records.

Subject Exclusion Criteria

Worker records not meeting the above matching criteria were excluded from analysis. Additionally, workers with non-invasive, including in situ, tumors were excluded from the study as these neoplasms are not expected to be fatal. We hypothesized that workers with multiple primary tumors may have different mortality experiences than workers with single primary neoplasms. Consequently, potential subjects with multiple primary cancers were excluded. Workers with diseases not included among the 18 sites listed in Table 1, which included cancers of the esophagus, stomach, colon and rectum, liver and intrahepatic bile duct (IBD), pancreas, larynx, lung and bronchus, skin melanoma and other malignant neoplasm including Kaposi's sarcoma (MN), breast, cervix uteri, corpus and uterus not otherwise specified (NOS), ovary and other uterine adnexa, prostate, testis, urinary bladder, kidney and renal pelvis, brain and other nervous system (ONS), and thyroid were also excluded. This was due to our inability to adequately differentiate these tumors at the three digit ICD level. Finally, workers whose cancers were identified by death certificate only (DCO) were excluded from analysis due to a lack of verifiable diagnostic data from the ICR.

Table 1. Selected SEER-defined major cancer site groups based on International Classification of Diseases (ICD) revisions 8-10 and ICD-Oncology revision 3 site codes.

Site	ICD-8 (1968-78)	ICD-9 (1979-98)	ICD-10 (1999+)	ICD-O-3
All cancers	140-207	140-208	C00-C97	C00-C77
Esophagus	150	150	C15	C15
Stomach	151	151	C16	C16
Colon & rectum	153-154	153-154	C18-C21	C18-C21
Liver & intrahepatic bile ducts (IBD)	155	155	C22	C22
Pancreas	157	157	C25	C25
Larynx	161	161	C32	C32
Lung & bronchus (including trachea)	162	162	C33-C34	C33-C34
Melanoma of skin & other non-epithelial malignant neoplasms including Kaposi's sarcoma (MN)	172, 173	172, 173	C43, C44, C46	C44
Breast	174	174-175	C50	C50
Cervix uteri	180	180	C53	C53
Corpus & uterus, not otherwise specified (NOS)	182	179, 182	C54-C55	C54-C55
Ovary & other uterine adnexa	183	183	C56-C57	C56-C57
Prostate	185	185	C61	C61
Testis	186	186	C62	C62
Urinary bladder	188	188	C67	C67
Kidney & renal pelvis (including ureter & other urinary organs)	189	189	C64-65, C66, C68	C64-65, C66, C68
Brain & other nervous system (ONS)	191-192	191-192	C70, C71, C72	C70, C71, C72
Thyroid	193	193	C73	C73

SOURCES: NCHS. (2007a). *Each cause list (ICD-10).* Retrieved 06/20, 2008, from ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10/;

NCI. (2004). *SEER cause of death recode 1969+ (9/17/2004).* Retrieved 06/20, 2008, from http://seer.cancer.gov/codrecode/1969+_d09172004/index.html;

NCI. (2003). *SEER site recode ICD-O-3 (1/27/2003) definition.* Retrieved 06/20, 2008, from http://seer.cancer.gov/siterecode/icdo3_d01272003/;

NCHS. (2007b). *ICD title & code cross reference file.* Retrieved 06/20, 2008, from http://www.cdc.gov/nchs/data/statab/gmwki_98.pdf

METHODS

Determination of UCOD and ACC

As stated previously, cause of death information for cohort members was ascertained from the mortality database provided to the ICR by the IDPH. DC-reported COD information included: 1) the immediate cause of death, defined as the final disease or condition resulting in death (e.g., an organ system failure, a neoplasm, injury, etc.); 2) a sequential list of conditions leading to the immediate cause that culminates with the UCOD, defined as the disease or injury that initiated the chain of events resulting in death; and 3) a list of other significant conditions contributing to death, but not resulting in the UCOD (NCHS, 2003). These contributing causes and significant other conditions are referred to as "All Conditions Coded" (ACC) by the IDPH and the NCHS. All medical conditions were coded by nosologists at the IDPH to the ICD revision in use at the time of death: ICD-8 for cohort deaths before 1979, ICD-9 for deaths occurring from 1979-1998, and ICD-10 for deaths since 1999. This study will compare the UCOD individually, as well as ACC, to the site of the first primary cancer identified by the ICR. For purposes of this study, ACC will include the UCOD.

Identification of Incident Cancer Cases

Cancer diagnoses identified by the ICR were coded to the ICD for Oncology (ICD-0) revision in use at the time of diagnosis. The ICR has subsequently updated all ICD-O codes to ICD-O-3, the most current revision. These diagnoses will be compared to the UCOD and ACC in the ICD mortality code revision in use at the time of the worker's death. Corresponding COD codes and ICD-O-3 site codes are presented in Table 1.

Survival Time

Survival time after cancer diagnosis was calculated by subtracting the worker's date of diagnosis from the date of death recorded by the ICR. ICR data routinely include only month and year of diagnosis. All workers were assigned a mid-range value of 15 for day of diagnosis. The mid-range value of the year (6 months) will be used for workers with a missing value for month of diagnosis.

Statistical Analyses

SAS 9.1 statistical software (SAS Institute Inc., Cary, NC) was used for all statistical analyses. Descriptive statistics on age at diagnosis, ICD revision in use at time of death, diagnosis era, race, gender, and survival time after cancer diagnosis calculated for all study subjects are presented in Tables 2 and 3.

Specific Aim I - Sub Aim 1

Analyses for this aim compared the UCOD from the IDPH mortality database to cancer incidence information from the ICR for the time frame and study population previously described. To evaluate the extent of agreement, we compared the UCOD to the site of the first primary malignant neoplasm identified by the ICR for 18 specific cancers listed in Table 4. As described above, ICR data served as the reference, or "gold standard," for these analyses. The DC mortality data and ICR cancer incidence data were considered to agree if the UCOD was equivalent to the ICD-O-3 site code recorded by the ICR. The findings were tabulated in a series of 2 * 2 tables. Sensitivity and predictive value-positive (PV+) were chosen as measures of agreement between the UCOD and the cancer incidence data reported by the ICR. Information was also tabulated in Table 4 for records that contained an UCOD which did not match the ICD-O-3 site code.

The exact binomial test was used to test for differential misclassification. These analyses are similar in nature to methodologies used by other researchers to evaluate agreement between different sources of diagnostic information, including the use of SEER Registries as a "gold standard" reference (Field et al., 2004; Sigurdson et al., 2003; Demers et al., 1992; Percy et al., 1990b).

The analyses adhered to the following definitions for sensitivity and PV+. Sensitivity was the probability that a study subject had a site-specific cancer listed as the UCOD given that the same disease was identified by the ICR as the worker's first primary malignant neoplasm. Sensitivity was calculated as a proportion, with the number of workers with a specific cancer reported as the UCOD that matched the diagnosis from ICR records in the numerator, and the total number of study subjects identified by the ICR with that particular cancer in the denominator.

PV+ was the probability of occurrence of a particular cancer, given its identification as the UCOD. In this study, PV+ was the count of workers with a specific cancer reported as the UCOD, which agrees with ICR records, in the numerator and the total number of workers with that cancer listed as the UCOD on their DCs in the denominator. PV+ is population-specific; its calculation depends on the prevalence of the disease in question among the population under study. Predictive value-positive also depends on the sensitivity and specificity of the "test" being evaluated, in this study, the UCOD or ACC on the DC. Sensitivity is generalizable. Alternatively, sensitivity is generally not affected by disease prevalence.

As Field et al. (2004) noted in a study that employed a similar cross-classification, sensitivity and PV+ provide the clearest indication of agreement in the comparison of

cancer diagnoses because they measure the probability of correctly reflecting the occurrence of a site-specific neoplasm. Other commonly reported measures, such as percent exact agreement, specificity, and predictive value-negative share a common limitation. All of these metrics would be dominated by the very large proportions of negative agreement for each neoplasm. The numbers of workers without the disease in question for which the UCOD and the ICR agree would overwhelm the ability of the metrics to discern any meaningful relationship between DC information and site-specific cancer occurrence. The results of these analyses would not be informative and therefore were not calculated for Specific Aim I.

Specific Aim I - Sub Aim 2

Analyses for this aim compared ACC from the IDPH mortality database to cancer incidence information from the ICR for the time frame and study population previously described. For the purposes of this study, ACC included the UCOD. Since records in this data set may contain multiple underlying and contributing causes of death as well as associated conditions, ACC was dichotomized as either matching or not matching the ICR incidence site code. For ACC, if a COD code corresponding to the ICD-O-3 site code recorded by the ICR appeared anywhere among the list of causes and associated conditions listed on the DC, it was considered a match. Including multiple cancer-related causes of death and associated conditions per record would have effectively increased the denominator for the calculation of sensitivity, underestimating this measure of agreement. Additionally, since only matching data are recorded among ACC for each specific disease, PV+s were not quantifiable.

Analyses for Aim I - Sub Aim 2 mirrored the analyses performed for Aim I - Sub Aim 1 with one exception. Since multiple conditions could be listed in the death records, ACC was considered to agree with ICR incidence data if a COD code equivalent to the ICR site code was found anywhere among ACC. Unlike the UCOD versus site code comparison, which resulted in a one-to-one matching, ACC created multiple opportunities for an individual record to match site codes from the ICR. For example, if a worker had more than one cancer listed among ACC, only the COD code corresponding to the cancer incidence site code recorded by ICR would generate a match, but any other conditions listed among ACC would generate "false-positive" results, which would invalidate the calculation of PV+ and underestimate sensitivity. Limiting agreement by ACC versus ICR site codes to records that match on those criteria effectively eliminated the opportunity to have any "false positives," which also invalidated the calculation of PV+s. Consequently only sensitivity was calculated for ACC and presented in Table 5.

Specific Aim II - Sub Aim 1

For Sub Aim 1 of both Specific Aims II and III, a logistic regression model was constructed to examine the effects of survival time, age at diagnosis, ICD revision in use at time of death, diagnosis era, race, and gender on the odds of agreement between cancer occurrences reported as the UCOD on DCs versus cancer incidence recorded by the ICR for the study population. Forward, backward, and stepwise model selection procedures were carried out using the Wald test as the primary selection criteria. According to Hosmer and Lemeshow (2000) the Wald test compares the maximum likelihood estimate of the slope parameter for the variable being considered to an estimate of the standard

error of the *beta* coefficient, resulting in a z-score for the probability that the variable makes a significant contribution to the model.

The outcome of interest was the odds that the UCOD would correspond to the ICD-O-3 site code recorded by the ICR for cohort members, given the values of several variables hypothesized to be possible predictors of agreement. The response was an indicator variable assigned a value of one if UCOD matched the ICR site code or zero, if UCOD was anything else.

Survival time after diagnosis was calculated as a continuous variable by subtracting the worker's date of cancer diagnosis from the date of death recorded by ICR. ICR records included the day, month, and year of death from the IDPH mortality database for all subjects, but only the month and year of diagnosis. All study subjects were assigned a mid-range value of 15 for day of diagnosis. Other variables in the full model included age at diagnosis, ICD revision in use at time of death, diagnosis era, gender, and race.

Age at diagnosis was originally a discrete variable with a value equal to the worker's age at last birthday. Since three different ICD revisions had been used to code CODs during the 33-year study time frame, we used the ICD revision in place at the time of the worker's cancer diagnosis. ICD-8 was used for a cancer diagnosis occurring from 1973-1978; ICD-9 from 1979-1998, and ICD-10 from 1999-2005. To evaluate the possible effects of medical changes over the study time frame, the workers were divided into tertiles based on the worker's year of diagnosis.

Specific Aim II - Sub Aim 2

Analyses for this aim compared agreement between ACC from the IDPH mortality database to cancer incidence information from the ICR for the time frame and study population previously described. In this study when assessing agreement between ACC and the ICR cancer incidence data, ACC included the UCOD. The analyses for Aim II - Sub Aim 2 mirrored the analyses performed for Aim II, Sub Aim 1.

Similar to the procedure for Aim II Sub-aim 1, another logistic regression model was constructed for Sub Aim 2 of Aims II and III to examine the effects of survival time, age at diagnosis, ICD revision in use at time of death, diagnosis era, race, and gender on the odds of agreement between cancer occurrences listed among ACC on DCs versus cancer incidence recorded by the ICR for the study population. Forward, backward, and stepwise model selection was carried out with the Wald test as the primary selection criteria. The outcome of interest was the odds that any condition listed among ACC would correspond to the ICD-O-3 site code recorded by the ICR for cohort members, given the values of several variables hypothesized to be possible predictors of agreement. The response was an indicator variable assigned a value of one if a COD code included in ACC matched the ICR site code or zero, if a corresponding code was not found among ACC. Model selection followed the procedures previously described. A continuous variable for survival time was included in the selection process. Age at diagnosis, diagnosis era, ICD revision in use at the time of death, gender, and race were evaluated as categorical variables.

Specific Aim III - Sub Aim 1

Analyses for Aim III Sub Aim 1 mirrored the analyses for Aim 2 Sub Aim 1. Multivariable logistic regression was used to examine whether other factors besides survival time affected the relationship between UCOD and cancer incidence data recorded by the ICR.

Specific Aim III - Sub Aim 2

Analyses for Aim III, Sub Aim 2 compared differences in agreement between ACC from the IDPH mortality database to cancer incidence information from the ICR for the time frame and study population previously described. In this study when assessing agreement between ACC and the ICR cancer incidence data, ACC included the UCOD. The analyses for Aim III, Sub Aim 2 mirrored the analyses performed for Aim III, Sub Aim 1.

RESULTS

Sample Size

Two thousand six hundred eighty-four (2,684) former IAAAP workers out of a total of 36,953 IAAAP workers (7.3%) were identified as having both an ICR-ascertained diagnosis of cancer as well as a death certified by the IDPH between January 01, 1973 and December 31, 2005. Eighty-nine (89) workers with non-invasive (including *in situ*) cancer and 411 eligible workers with multiple primary cancers were excluded from the study. An additional 482 workers who had tumors which were not distinguishable at the three digit ICD level (e.g., cancers of the oral cavity and pharynx, Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, and leukemia) were excluded from the study. Finally, 52 workers whose cancers were identified by death certificate only (DCO) were excluded from analysis due to a lack of verifiable diagnostic data from the ICR. The sets of workers excluded from analysis were not mutually exclusive. One hundred forty-five (145) workers met more than one criterion. A total of 1,795 workers, registered by the ICR with a single first primary malignant neoplasm between January 01, 1973 and December 31, 2005, whose deaths were also certified by the IDPH during the same time period, were included in the study.

Demographic data, supplied by the ICR, as well as cancer incidence data for the study subjects are presented in Table 2. The study cohort was composed predominantly of males (70%) and was overwhelmingly white, with only about 2% black. ICD-8, -9, and -10 were used to code approximately 15, 68, and 17% of the diseases, respectively. Almost 41% of workers were registered by the ICR during the middle diagnostic era, with nearly 29% in the first era, and 30% during the final era.

Table 2. Demographic information for the 1,795 IAAAP cohort members identified by the ICR with a first primary incident malignant neoplasm between 1973 and 2005 and matched to mortality information provided by IDPH for the same time period.

Characteristic	**n**	**%**
Gender		
Male	1260	70.2
Female	535	29.8
Race		
White	1753	97.7
Black	40	2.2
American Indian, Aleutian, Eskimo	1	0.1
Invalid code	1	0.1
ICD revision		
ICD-8 (1973-1978)	268	14.9
ICD-9 (1979-1998)	1222	68.1
ICD-10 (1999-2005)	305	17.0
Diagnosis Era		
1973-1983	518	28.9
1984-1994	731	40.7
1995-2005	546	30.4

Descriptive statistics for age at diagnosis, age at death, and survival time are presented in Table 3. The mean and median age at diagnosis was 67 and 68 years, respectively, with a range from 22 to 95 years. The mean and median age at death was 69 and 70 years, respectively, with a minimum of 32 and maximum of 100 years. Sixteen (16) workers had missing values for month of diagnosis. These workers were assigned mid-range values of six months. These assumptions resulted in negative survival time values for approximately one percent of the cohort. The lowest one percent of survival times was approximately negative two days. The minimum survival time was

approximately negative 101 days. Median survival time was slightly less than one year and the maximum was nearly 30 years.

Table 3. Descriptive information for the IAAAP cohort* identified by the ICR with a first primary incident malignant neoplasm between 1973 and 2005 and matched to mortality information provided by IDPH for the same time period.

Characteristic	n	Mean ±(SD)	Minimum	Q1	Median	Q3	Maximum
Age at diagnosis	1,795	66.8 (11.2)	22	60	68	74	95
Age at death	1,795	69.5 (11.3)	32	62	70	77	100
Survival (years)	1,795	2.6 (4.2)	-0.3	0.3	1.0	3.0	29.8

*Sixteen workers had missing month of diagnosis; mid-range value of year (six months) was assigned.

Specific Aim I Results

Table 4 presents a cross classification of UCOD versus ICR incidence site code showing frequencies and percentages for each of the 18 diseases studied. Lung cancer was the most frequently recorded disease with 739 incident cases which comprised 41% of the ICR registrations among the study cohort. Lung cancer was listed as the UCOD on 635 DCs, with 628 matching ICR records. Incident cancers of the colon and rectum were recorded by the ICR for 265 (15%) of cohort members. One hundred fifty-nine (159) DCs recorded colon and rectum cancer as the UCOD, of which 154 agreed with the ICR. Two hundred eleven (211) cases of prostate cancer accounted for 12% of ICR records and prostate cancer was listed as the UCOD on 82 DCs, all of which matched ICR records. Breast cancer, which included both genders, was the fourth most frequently occurring disease among this cohort, with 112 (6.2%) of cases recorded by the ICR. ICR records indicated that three cases (0.2%) of breast cancer occurred among male cohort members. Overall, breast cancer was listed as the UCOD on 70 DCs, which all agreed

with ICR records. No DC listed breast cancer as an UCOD for a male worker. Eighty-seven (87) cases of pancreatic cancer were recorded by the ICR, which accounted for 4.9% of the cohort. Seventy-four (74) of 77 DCs with pancreatic cancer listed as the UCOD agreed with ICR incidence data. The remaining 13 cancers each had 60 or fewer incident cases registered by the ICR.

The same five cancers (i.e., lung, colon and rectum, prostate, breast, pancreas) were most frequently listed as the UCOD; however breast and pancreatic cancer switched ranks. Table 4 includes “false positive” results, diseases that were recorded as the UCOD, but failed to match the incidence site code recorded by the ICR for that worker. Additionally, 525 (29.3%) workers had incident cancers recorded by the ICR which were not listed as the UCOD on the worker’s DC.

Table 4. Cross-classification of UCOD from DC and site of first incident primary malignant neoplasm reported by ICR.

Cancer identified as UCOD Frequency %	First Malignant Primary Tumor Site Identified by Iowa Cancer Registry																		
	Esophagus	Stomach	Colon & rectum	Liver & IBD	Pancreas	Larynx	Lung & bronchus	Skin melanoma & other MN	Breast	Cervix uteri	Corpus & uterus, NOS	Ovary & uterine adnexa	Prostate	Testis	Urinary bladder	Kidney & renal pelvis	Brain & ONS	Thyroid	Total
Esophagus	30 1.7	4 0.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	34 1.9
Stomach	1 0.1	16 0.9	1 0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	18 1.0
Colon & rectum	-	1 0.1	154 8.6	-	2 0.1	-	2 0.1	-	-	-	-	-	-	-	-	-	-	-	159 8.9
Liver & IBD*	-	-	1 0.1	12 0.7	1 0.1	-	1 0.1	-	-	-	-	-	-	-	-	-	-	-	15 0.8
Pancreas	-	-	-	1 0.1	74 4.1	-	2 0.1	-	-	-	-	-	-	-	-	-	-	-	77 4.3
Larynx	-	-	-	-	-	7 0.4	-	-	-	-	-	-	-	-	-	-	-	-	7 0.4
Lung & bronchus	1 0.1	1 0.1	2 0.1	-	-	1 0.1	628 35.0	-	-	-	-	-	2 0.1	-	-	-	-	-	635 35.4
Skin melanoma & other MN**	-	-	-	-	-	1 0.1	-	13 0.7	-	-	-	-	-	-	-	-	-	-	14 0.8
Breast	-	-	-	-	-	-	-	-	70 3.9	-	-	-	-	-	-	-	-	-	70 3.9
Cervix uteri	-	-	-	-	-	-	-	-	-	16 0.9	-	-	-	-	-	-	-	-	16 0.9
Corpus & uterus, NOS***	-	-	-	-	-	-	-	-	-	4 0.2	9 0.5	-	-	-	-	-	-	-	13 0.7
Ovary & other uterine adnexa	-	-	-	-	-	-	-	-	-	-	-	21 1.2	-	-	-	-	-	-	21 1.2
Prostate	-	-	-	-	-	-	-	-	-	-	-	-	82 4.6	-	-	-	-	-	82 4.6
Testis	-	-	-	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	0
Urinary bladder	1 0.1	-	1 0.1	-	-	-	-	-	-	-	-	-	-	-	25 1.4	2 0.1	-	-	29 1.6
Kidney & renal pelvis	-	-	-	-	-	-	1 0.1	-	-	-	-	-	1 0.1	-	2 0.1	33 1.8	-	-	37 2.1
Brain & ONS****	-	-	-	-	-	-	3 0.2	-	1 0.1	-	-	-	-	-	-	-	37 2.1	-	41 2.2
Thyroid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 0.11	2 0.1
ICR site code not listed as UCOD	7 0.4	4 0.2	106 5.9	2 0.1	10 0.6	17 1.0	102 5.7	14 0.8	41 2.3	6 0.3	13 0.7	5 0.3	126 7.0	5 0.3	33 1.8	22 1.2	5 0.3	7 0.4	525 29.3
Total	40 2.3	26 1.5	265 14.8	15 0.8	87 4.9	26 1.5	739 41.2	27 1.5	112 6.2	26 1.5	22 1.2	26 1.5	211 11.8	5 0.3	60 3.3	57 3.2	42 2.3	9 0.5	1795 100.0

*IBD = intrahepatic bile ducts
**MN = malignant neoplasm
***NOS = not otherwise specified
****ONS = other nervous system

Since ACC contained up to 14 causes and contributing factors, we were unable to include “false positives” among the cross classifications presented in Table 5. Workers for whom ACC included one or more codes that may have matched an ICD-O-3 site code for one of the 18 diseases studied, but which did not include a code that corresponded to the incidence site code recorded by the ICR for that worker, were counted among the bottom row of Table 5, “ICR site code not among ACC.” This category also included workers whose DCs did not list any cancers that were among the 18 diseases of interest in this study as well as workers for whom the DC listed no cancer-related COD or associated condition. Matching between ACC and ICR site code was not dramatically different compared to UCOD. Raw frequencies of matching between ACC and ICR data were higher, compared to UCOD, for all but six cancers (i.e., liver and intrahepatic bile ducts (IBD), cervix uteri, corpus and uterus, not otherwise specified (NOS), testis, brain and other nervous system (ONS), and thyroid.) However these six diseases were reported infrequently by both the ICR and DCs. The two rarest cancers among IAAAP workers were testicular cancer, which was recorded five times by the ICR, but was never listed as an UCOD or among ACC and thyroid cancer, with only nine occurrences, two of which were listed as an UCOD. Additionally, 452 (25.2%) incident cancers were not listed among ACC on the corresponding DCs.

Table 5. Cross-classification of ACC on DC and site of first incident primary malignant neoplasm reported by the ICR.

Cancers identified among ACC on DC Frequency %	First Malignant Primary Tumor Site Identified by Iowa Cancer Registry																		
	Esophagus	Stomach	Colon & rectum	Liver & IBD	Pancreas	Larynx	Lung & bronchus	Skin melanoma & other MN	Breast	Cervix uteri	Corpus & uterus, NOS	Ovary & uterine adnexa	Prostate	Testis	Urinary bladder	Kidney & renal pelvis	Brain & ONS	Thyroid	Total
Esophagus	34 1.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	34 1.9
Stomach	-	17 1.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17 1.0
Colon & rectum	-	-	178 9.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	178 9.9
Liver & IBD*	-	-	-	12 0.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12 0.7
Pancreas	-	-	-	-	76 4.2	-	-	-	-	-	-	-	-	-	-	-	-	-	76 4.2
Larynx	-	-	-	-	-	9 0.5	-	-	-	-	-	-	-	-	-	-	-	-	9 0.5
Lung & bronchus	-	-	-	-	-	-	665 37.1	-	-	-	-	-	-	-	-	-	-	-	665 37.1
Skin melanoma & other MN**	-	-	-	-	-	-	-	14 0.8	-	-	-	-	-	-	-	-	-	-	14 0.8
Breast	-	-	-	-	-	-	-	-	79 4.4	-	-	-	-	-	-	-	-	-	79 4.4
Cervix uteri	-	-	-	-	-	-	-	-	-	16 0.9	-	-	-	-	-	-	-	-	16 0.9
Corpus & uterus, NOS***	-	-	-	-	-	-	-	-	-	-	9 0.5	-	-	-	-	-	-	-	9 0.5
Ovary/other uterine adnexa	-	-	-	-	-	-	-	-	-	-	-	22 1.2	-	-	-	-	-	-	22 1.2
Prostate	-	-	-	-	-	-	-	-	-	-	-	-	109 6.1	-	-	-	-	-	109 6.1
Testis	-	-	-	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	0
Urinary bladder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	27 1.5	-	-	-	27 1.501
Kidney & renal pelvis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	37 2.1	-	-	37 2.1
Brain & ONS****	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	37 2.1	-	37 2.1
Thyroid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 0.1	2 0.1
ICR site not among ACC	6 0.3	9 0.5	87 4.9	3 0.2	11 0.6	17 1.0	74 4.1	13 0.7	33 1.8	10 0.6	13 0.7	4 0.2	102 5.7	5 0.3	33 1.8	20 1.1	5 0.3	7 0.4	452 25.2
Total	40 2.2	26 1.5	265 14.8	15 0.8	87 4.9	26 1.5	739 41.2	27 1.5	112 6.2	26 1.5	22 1.2	26 1.5	211 11.8	5 0.3	60 3.3	57 3.2	42 2.3	9 0.50	1795 100.0

*IBD = intrahepatic bile ducts
**MN = malignant neoplasm
***NOS = not otherwise specified
****ONS = other nervous system

The sensitivity of UCOD relative to the site of the first incident primary cancer reported by the ICR, presented in Table 6, ranged from zero percent for testicular cancer to 88.1% for brain and ONS malignancies. Besides brain and ONS, five other cancers including esophageal, liver and IBD, pancreatic, lung and bronchus, and ovary and other uterine adnexa, had sensitivities of 75% or greater. Five cancer types (stomach, colon and rectum, breast, cervix uteri, and kidney and renal pelvis) had sensitivities from 57.9-62.5%. The remaining seven cancer types listed in Table 6 (laryngeal, skin melanoma and other MN, corpus and uterus NOS, prostate, testicular, urinary bladder, and thyroid) had sensitivities less than 50%. PV+s were uniformly higher than sensitivities, except for an indeterminable result for testicular cancer and a PV+ value (80%) equal to the sensitivity value for liver and IBD. Only the PV+ value (69%) for cancer of the corpus and uterus NOS fell below 80%.

Table 6. Sensitivity and predictive value positive (PV+) of the UCOD reported on DCs relative to the site of first incident primary cancer reported by the ICR.

UCOD	Sensitivity	PV+
Esophagus	75.0	88.2
Stomach	61.5	88.9
Colon & rectum	58.1	96.9
Liver & IBD	80.0	80.0
Pancreas	85.1	96.1
Larynx	26.9	100
Lung & bronchus	85.0	98.9
Skin melanoma & other MN	48.2	92.9
Breast	62.5	100
Cervix uteri	61.5	100
Corpus & uterus, NOS	40.9	69.2
Ovary & other uterine adnexa	80.8	100
Prostate	38.9	100
Testis	0.0	Und#
Urinary bladder	41.7	86.2
Kidney & renal pelvis	57.9	89.2
Brain & ONS	88.1	90.2
Thyroid	22.2	100

Undefined - no cases identified as UCOD

We hypothesized that DCs would under-report cancer incidence compared to the ICR incidence data. To evaluate the degree of under-reporting for specific diseases, the complement of sensitivity, termed percent under-reported, was calculated. Table 7 presents the results in rank order. Percent under-reported by UCOD ranged from 11.9% for brain and ONS to 100% for testicular cancer. P-values were calculated using the exact binomial test for differential misclassification. Frequency of incidence diagnosis by the ICR is also presented.

Table 7. Percent under-reported by the UCOD reported on DCs relative to the site of first incident primary cancer reported by the ICR.

UCOD	% Under reported	p-value*	ICR - N
Brain & ONS	11.9	1.000	42
Pancreas	14.9	0.021	87
Lung & bronchus	15.0	<.001	739
Ovary & other uterine adnexa	19.2	0.063	26
Liver & IBD	20.0	1.000	15
Esophagus	25.0	0.180	40
Breast	37.5	<.001	112
Stomach	38.5	0.039	26
Cervix uteri	38.5	0.002	26
Colon & rectum	41.9	<.001	265
Kidney & renal pelvis	42.1	<.001	57
Skin melanoma & other MN	51.8	<.001	27
Urinary bladder	58.3	<.001	60
Corpus & uterus NOS	59.1	0.049	22
Prostate	61.1	<.001	211
Larynx	73.1	<.001	26
Thyroid	77.8	0.016	9
Testis	100.0	0.063	5

* p-values calculated using two-sided exact binomial test

Sensitivities of ACC relative to the site of the first incident primary cancer reported by the ICR were higher than corresponding measures for UCOD, with the exception of testicular, thyroid, cervix uteri, brain and ONS, corpus and uterus NOS, and liver and IBD diseases, which remained unchanged (Tables 6 and 7). Because ACC included UCOD a decrease in sensitivity was not possible.

Twelve (12) diseases had totals of fewer than 20 workers in the cells representing the discordant pairs in the 2 * 2 tables constructed to evaluate the sensitivity and PV+ of the UCOD or ACC relative to ICR data. The exact binomial test was used to test for

differential misclassification among all diseases (Table 7 for UCOD and Table 9 for ACC). P-values failed to reject the null hypothesis of nondifferential misclassification of cancer incidence site code by the UCOD at the $\alpha = 0.05$ level for five diseases: esophagus, liver and IBD, ovary and other uterine adnexa, testis, and brain and ONS cancers. The null hypothesis of nondifferential misclassification of ICD-O-3 site code by ACC on the DC was not rejected for eight diseases including: esophageal, stomach, liver and IBD, pancreatic, corpus and uterus NOS, ovary and other uterine adnexa, testicular, and brain and ONS cancers.

Table 8. Sensitivity of ACC on DCs relative to the site of first incident primary cancer reported by the ICR.

All conditions coded	Sensitivity
Esophagus	85.0
Stomach	65.4
Colon & rectum	67.2
Liver & IBD	80.0
Pancreas	87.4
Larynx	34.6
Lung & bronchus	90.0
Skin melanoma & other MN	51.9
Breast	70.5
Cervix uteri	61.5
Corpus & uterus, NOS	40.9
Ovary & other uterine adnexa	84.6
Prostate	51.7
Testis	0.0
Urinary bladder	45.0
Kidney & renal pelvis	64.9
Brain & ONS	88.1
Thyroid	22.2

ACC also under-reported cancer incidence compared to the ICR (Table 9), but as would be expected, to a lesser degree for 12 diseases (esophageal, stomach, colon and rectal, pancreatic, laryngeal, lung and bronchus, skin melanoma and other MN, breast, ovary and other uterine adnexa, prostatic, urinary bladder, and kidney and renal pelvis cancers) than was observed for the UCOD alone. Results were calculated in the same manner as they were for the UCOD. Including ACC, as compared to UCOD alone, changed the rank order of the various cancers slightly. For example, the degree of under-reporting for cancer of the lung and bronchus decreased by 5%, which moved its rank up two spots.

Table 9. Percent under-reported by ACC on DCs relative to the site of first incident primary cancer reported by the ICR.

ACC	% Under reported	p-value*	ICR - N
Lung & bronchus	10.0	<0.001	739
Brain & ONS	11.9	1.000	42
Pancreas	12.6	0.057	87
Esophagus	15.0	0.754	40
Ovary & other uterine adnexa	15.4	0.125	26
Liver & IBD	20.0	1.000	15
Breast	29.5	<0.001	112
Colon & rectum	32.8	<0.001	265
Stomach	34.6	0.065	26
Kidney & renal pelvis	35.1	0.004	57
Cervix uteri	38.5	0.002	26
Skin melanoma & other MN	48.1	0.002	27
Prostate	48.3	<0.001	211
Urinary bladder	55.0	<0.001	60
Corpus & uterus NOS	59.1	0.167	22
Larynx	65.4	<0.001	26
Thyroid	77.8	0.016	9
Testis	100.0	0.063	5

* p-values calculated using two-sided exact binomial test

Specific Aims II and III Results

Multivariable logistic regression modeling was performed for Specific Aims II and III. Sub Aim 1 for both Aims examined the effect of survival time as well as several other variables on agreement between UCOD and ICR site code. Sub Aim 2 for both Aims evaluated agreement between ACC and site code given the same set of possible predictors. The outcome of interest in both models was the odds of correctly matching DC information to cancer incidence data from the ICR.

Survival time was a continuous variable in both models. Age at diagnosis was originally a discreet variable. Quartiles of the integral values were calculated (22-60, 61-68, 69-74, 75 or more years) and both models were re-run with age at diagnosis as a class variable, which produced lower Akaike Information Criterion (AIC) scores. AIC is a goodness of fit measure that is based on the likelihood function and adjusts for the number of parameters in the model. The smaller the AIC value, the better the model is considered to fit the data (Kleinbaum, Kupper, Nizam, & Muller, 2008).

Model selection progressed with age at diagnosis as a class variable. Since three different ICD revisions had been used to code CODs during the 33-year study time frame, we were interested in whether either changing ICD revisions or advances in cancer diagnostics and treatment over time could confound the relationships between DC and cancer incidence data. To evaluate the possible effects of medical changes over the study time frame, the year of diagnosis was categorized in tertiles. ICD revision and diagnosis era, were each tested as possible predictors in the models. The models including diagnosis era had lower AIC scores compared to the models with ICD revision, so ICD revision was eliminated from consideration for both regression equations.

A p-value of 0.25 was used as the cutoff for inclusion during univariate analysis (Hosmer & Lemeshow, 2000). All model selection procedures indicated that the continuous variable for survival time (survtimeyr) and the categorical variable for age at diagnosis (agedxcat) were the only statistically significant predictors, at the $\alpha = 0.05$ level, of matching UCOD and ICR site code in both models. Diagnosis era (era,) gender (genind,) and race were not found to be statistically significant predictors of agreement between UCOD or ACC and ICR site code.

For the UCOD model, an interaction term for age at diagnosis and survival time was added, but it did not make a statistically significant contribution to the model's ability to predict agreement between UCOD and ICR site code. The Hosmer-Lemeshow goodness of fit test (H-L) also indicated a lack of fit, so the interaction term was removed from the UCOD model. Hosmer and Lemeshow (2000), define goodness of fit as a measure of how well the regression model describes the outcome variable. The H-L test is based on the null hypothesis that the model fits the data well, so failure to reject the null hypothesis indicates an adequate fit. The H-L test was conducted at the 5% level of statistical significance. The model without the interaction term still failed H-L, so gender and era, neither of which had been individually significant, were re-introduced, resulting in a model that fit the data at the 5% level of significance. This improved the H-L results from 0.0032 for the reduced model to 0.1049. The final model was:

$$\ln[p/(1-p)] = 1.6166 - (0.2089 * \text{survtimeyr}) + (0.5625 * \text{agedxcat1}) + (0.3711 * \text{agedxcat2}) - (0.3572 * \text{agedxcat3}) - (0.3330 * \text{genind}) - (0.0825 * \text{era1}) - (0.0369 * \text{era2}).$$

Regression assumptions were evaluated using plots of Pearson and deviance residuals. The plots indicated constant variance with no discernible patterns.

Results of the regression modeling to predict the odds ratio, with 95% confidence intervals, of agreement between UCOD and ICR incidence data are presented in Table 10. A one-year increase in survival time was found to decrease the odds of agreement to 0.812. Odds ratios of agreement for members of the 22-60 and 61-68 year old age at diagnosis groups were 3.124 and 2.579 respectively compared to the oldest age at diagnosis group, 75 or more years. Odds of agreement for the 69-74 year old age at diagnosis group were estimated to be 1.245, which was not significantly different than the odds of agreement for the 75 or more year old age group. Male workers had odds of agreement of 0.717 compared to females. Finally, workers diagnosed during 1973-1983 and 1984-1994 had odds ratios of agreement of 0.817 and 0.855, respectively, compared to workers diagnosed during 1995-2005. Odds of agreement did not differ significantly for either diagnosis era compared to the reference era.

Table 10. Logistic regression of agreement between UCOD and ICR incidence data modeled by survival time, age at diagnosis, gender, and diagnosis era.

Variable	OR (95% CI)	p-value#
Survival time (1 year increase)	0.812 (0.786-0.838)	<0.001
Age at diagnosis (years)		<0.001
22-60	3.124 (2.261-4.315)	
61-68	2.579 (1.887-3.526)	
69-74	1.245 (0.931-1.664)	
≥75	*	
Gender		0.008
Male	0.717 (0.560-0.917)	
Female	*	
Diagnosis era		0.372
1973-1983	0.817 (0.604-1.107)	
1984-1994	0.855 (0.656-1.116)	
1995-2005	*	

* Reference level
# p-values calculated using the Wald test

ACC model selection followed the procedures previously described. Age at diagnosis was evaluated as a categorical variable. Results indicated that era, race, ICD revision, and gender are not statistically significant predictors of agreement between ACC and ICR site code. All selection procedures chose the same reduced model with the continuous variable for survival time and the categorical variable for age at diagnosis. The term for interaction between age at diagnosis and survival time was not a statistically significant predictor of agreement and the H-L test indicated a lack of fit. A quadratic term on survival time ($survtimeyr^2$) showed a significant effect; however the model failed to pass H-L. After reintroducing gender, the model passed H-L with a score of 0.1475. The final model was:

$$\ln[p/(1-p)] = 1.9828 - (0.2832 * survtimeyr) + (0.4259 * agedxcat1) + (0.3304 * agedxcat2) - (0.3229 * agedxcat3) + (0.00533 * survtimeyr^2) - (0.2221 * genind).$$

Regression assumptions were evaluated using plots of Pearson and deviance residuals. The plots indicated constant variance with no discernible patterns.

Table 11 presents the results of the multivariate logistic regression modeling to estimate the odds ratio, with 95% confidence intervals, of agreement between ACC on the DC and cancer incidence data reported by the ICR. Since the model contained a quadratic term on survival time as well as a significant predictor variable for survival time, the Wald test was conducted to determine the significance of both coefficients in the model. One year of survival after cancer diagnosis was selected as the reference value. Increasing survival time in one year increments progressively decreased the odds of agreement between ACC and ICR cancer incidence data compared to the odds of agreement for survival time of one year. The odds ratios of agreement between ACC and ICR incidence data were 0.766, 0.592, and 0.463 for two, three, and four years of survival after cancer diagnosis respectively compared to the reference value of one year of survival after cancer diagnosis. Odds of agreement for members of the 22-60 and 61-68 year old age at diagnosis groups were 2.362 and 2.147, respectively, compared to the 75 or more years of age at diagnosis group. Odds of agreement for the 69-74 year old age at diagnosis group were estimated to be 1.117, which was not significantly different than the odds of agreement for the 75 or more year old age group. Male workers had an odds ratio of agreement of 0.801 compared to females.

Table 11. Logistic regression of agreement between ACC and ICR incidence data modeled by survival time, age at diagnosis, and gender.

Variable	OR (95% CI)	p-value#
Survival time (years)		<0.001
1	*	
2	0.766 (0.725-0.809)	
3	0.592 (0.534-0.657)	
4	0.463 (0.400-0.537)	
Age at diagnosis (years)		<0.001
22-60	2.362 (1.696-3.290)	
61-68	2.147 (1.537-2.997)	
69-74	1.117 (0.819-1.523)	
≥75	*	
Gender		0.094
Male	0.801 (0.618-1.038)	
Female	*	

* Reference level
# p-value calculated using the Wald test

DISCUSSION

The overall objective of the research was to assess the ability of DCs to reflect cancer incidence within a population of former DOD contract workers. As hypothesized in the Introduction, DCs under-reported cancer incidence as compared to cancer incidence reported by the ICR. Six of the 18 diseases evaluated in this study had sensitivities ranging between 75% and 88%, five diseases had sensitivities of approximately 60%, and seven cancers had sensitivities below 50% for the UCOD relative to the site of the first incident primary cancer reported by the ICR. To quantify the degree of under-reporting by the UCOD, the complement of the sensitivity relative to the ICR data, termed the percent under-reported, was calculated. For frequently occurring incident cancers, this measure likely provides a reliable estimate of how well the UCOD reflects cancer incidence.

Sensitivity of ACC was at least as good as or better than UCOD, which would be expected since ACC included UCOD. The variation in sensitivity between DC (UCOD or ACC) reported cancer information and ICR cancer incidence data is likely due to a complex interplay of numerous factors. These include the survival time after development of cancer, the tendency of certain primary cancer types to develop metastases in specific organs (Fokas, Engenhart-Cabillic, Daniilidis, Rose, and An, 2007; Chambers, Groom, and MacDonald, 2002) that have increased likelihood of being reported as the UCOD (e.g. colorectal cancers often metastasize to the lung or liver), cancer-related illnesses (e.g., lung cancer and pneumonia), and the severity of comorbid conditions (e.g., heart disease, pulmonary disease, etc.). Percy et al. (1981; 1990b) also

noted discrepancies in the validity of measures of agreement between DC reported cancer listings and cancer incidence data among different sites.

The cancer-related information provided by the addition of ACC relative to the site of the first incident primary cancer reported by the ICR increased the sensitivity for 12 cancer types (esophagus, stomach, colon and rectum, pancreas, larynx, lung and bronchus, skin melanoma and other MN, breast, ovary and other uterine adnexa, prostate, urinary bladder, kidney and renal pelvis), but showed no improvement for six types of cancer (testicular, thyroid, cervix uteri, brain and ONS, corpus and uterus NOS, and liver and IBD diseases) when ACC was added to the comparisons. Improvements in sensitivity of ACC over UCOD ranged from zero to slightly less than 13%. Several cancer types showed a modest increase, as compared to UCOD, in sensitivity when ACC were added. In fact, prostate cancer, esophageal cancer, colon and rectum cancer, breast cancer, and laryngeal cancer had sensitivity increases of 12.8%, 10.0%, 9.1%, 8.0%, and 7.7%, respectively when ACC was added. Under-reporting of cancer incidence by DC compared to ICR data improved by the same margins when ACC results were compared to under-reporting by the UCOD only.

The additional detection of these cancers may improve the validity of some types of epidemiologic analyses. For example, if a future nested case-control study was performed within the framework of the IAAAP Munitions Workers Retrospective Mortality Study, the additional ascertainment of lung cancer cases, achieved by using information in the ACC, would help improve the validity of the study. For the diseases in the highest sensitivity groups, the UCOD reflected 75% or more of the cancer incidence

ascertained by the ICR, while ACC predicted 80% or more of the incident cases recorded by the ICR among the IAAP worker cohort.

PV+ values indicated that if one of the 18 cancers evaluated in this study was listed as an UCOD, the worker was likely to have had that disease identified by the ICR. With the exception of testicular cancer, which was not listed on any DC, only cancer of the corpus and uterus NOS had a PV+ below 80% for the UCOD.

Sensitivity and PV+ are helpful measures of the agreement between DC information and data for cancer incidence obtained from the ICR. For example, in the case of lung cancer, the UCOD had a sensitivity of 85% relative to the ICR incidence data. This indicates that 85% (628/739) of workers that were identified by the ICR to have had a first incident primary lung cancer also had lung cancer listed as the UCOD on their DCs. The ICR identified 111 workers with a first incident primary lung cancer that had some other UCOD listed on their DCs. The PV+ for lung cancer compared to the ICR incidence data was 98.9%. This value indicates that of the 635 workers who had lung cancer listed as their UCOD, ICR records identified lung cancer as the first incident primary neoplasm for almost 99% (628) of those workers. These two values, taken together, suggest that the UCOD could likely be considered a reasonable indicator of incident lung cancer among the IAAAP cohort. The UCOD correctly reflected the incident disease in 85% of IAAAP workers who had lung cancer according to the ICR and almost 99% of cohort members who had lung cancer listed as their UCOD also had a malignant neoplasm of the lung recorded by the ICR.

However, for thyroid cancer, the UCOD had a sensitivity of only 22.2% relative to the ICR incidence data, indicating that 22% (2/9) workers who had a first incident case

of invasive thyroid cancer recorded by the ICR also had that disease listed as the UCOD on their DC. The 100% PV+ of the UCOD for thyroid cancer relative to the ICR incidence data reflects the fact that all of the workers who had thyroid cancer listed as the UCOD on their DC also had a first incident primary case of that disease according to the ICR records. These results imply that the UCOD correctly reflected the first primary malignancy for IAAAP workers whose deaths were attributed to thyroid cancer. However, for the majority of this very small sample, these cancers may not have been fatal and consequently the UCOD under-reported thyroid cancer incidence by 78% for this cohort.

We hypothesized that DCs would underestimate cancer incidence. Raw frequencies, presented in Table 4 indicate that UCOD underestimated cancer incidence for every disease compared to the ICR. This finding is in contrast to that of Percy et al. (1990b) which found under-reporting for 11 of approximately 60 cancer types evaluated. Differences compared to the Percy et al. (1990b) data may be due to variations in inclusion criteria. Percy et al. (1990b) required subjects to have a cancer-related cause of death on the DC, while this study, had no such requirement. Additionally, the studies by Percy et al. (1981; 1990b) calculated different measures of agreement than this study, so direct comparison should be made with caution.

Some over-reporting by UCOD compared to the ICR incidence data also occurred for 11 cancer types: esophagus, stomach, colon and rectum, liver and IBD, pancreas, lung and bronchus, skin melanoma and other MN, corpus and uterus NOS, urinary bladder, kidney and renal pelvis, and brain and ONS cancers. Percy et al. (1990b) also found over-reporting of esophageal and testicular cancer, as well as two other diseases which were

specified somewhat differently than in this study. Cancers without over-reporting by UCOD compared to ICR data included laryngeal, breast, cervix uteri, ovary and other uterine adnexa, prostate, testis, and thyroid.

The method used to indicate matching between ACC and cancer incidence site code did not count multiple CODs that may have been included on the DC. Table 5 presents frequencies for records with matching ACC and site code only. Using this method of matching ACC to site code also underestimated cancer incidence compared to the ICR incidence data, but did so to a lesser extent than using UCOD only. Reasons for misclassification, both over and under-reporting, are likely to include a similar list of possibilities as was hypothesized for the differences in sensitivity between UCOD and ACC, namely: a complex interplay of numerous factors including the survival time after development of cancer, the tendency of certain primary cancer types to develop metastases in specific organs (Fokas et al., 2007; Chambers et al., 2002) that have increased likelihood of being reported as the UCOD (e.g. colorectal cancers often metastasize to the lung or liver), cancer-related illnesses (e.g., lung cancer and pneumonia), and the severity of comorbid conditions (e.g., heart disease, pulmonary disease, etc.). Additionally, the small sample sizes for some cancer types in this study make it difficult to accurately estimate measures of agreement for DC data relative to ICR-reported cancer incidence data.

For this data set, the exact binomial test indicated that using the UCOD to reflect cancer incidence resulted in more differential misclassification, either over or under-reporting, than would be expected due to chance alone for 13 diseases. These included cancers of the stomach, colon and rectum, pancreas, larynx, lung and bronchus, skin

melanoma and other MN, breast, cervix uteri, corpus and uterus NOS, prostate, urinary bladder, kidney and renal pelvis, and thyroid. For the other five neoplasms (esophageal, liver and IBD, ovary and other uterine adnexa, testicular, and brain and ONS cancers), we have no evidence to indicate whether differential misclassification occurred more frequently than would be expected due solely to chance.

Under-reporting by the UCOD occurred more frequently than over-reporting for every disease except cancer of the liver and IBD, which had the same number of cases (three) both over and under-reported. The over-reports were actually cancers of the colon and rectum, pancreas, and lung and bronchus. One under-reported case was misclassified as pancreatic cancer and two cases were not listed anywhere on the DC.

The results for liver cancer are not totally unexpected. Percy, Ries, and Van Holten (1990a) point out a number of changes that occurred between ICD-8 and ICD-9 that affect the way primary and secondary cancers of the liver are coded. Because the liver is a frequent site of metastatic disease, these changes have the potential to significantly influence COD coding. By controlling for ICD revision, we attempted to evaluate whether these changes had any possible effect on our findings.

The exact binomial test indicated that differential misclassification of cancer incidence site code by ACC occurred more frequently than would be expected due to chance alone for ten diseases: colon and rectum, larynx, lung and bronchus, skin melanoma and other MN, breast, cervix uteri, prostate, urinary bladder, kidney and renal pelvis, and thyroid cancers. We have no evidence to indicate that differential misclassification occurred for the remaining eight cancers.

In this study, misclassification can take the form of either over or under-reporting of cancer incidence. Differential misclassification can increase the odds of either agreement or disagreement between DC data and cancer incidence information. If the misclassification is nondifferential, the frequency of both over and under-reporting should be approximately equal. Nondifferential misclassification should only have the effect of diluting the odds of agreement between DC data and cancer incidence data. Considering diseases for which the exact binomial test rejected the null hypothesis, of nondifferential misclassification, we can say that if DC data underestimated cancer incidence, that underestimation occurred more frequently than would be expected due to chance alone. Conversely, if the exact binomial test failed to reject the null hypothesis that any misclassification was nondifferential, we have no evidence to say that the over or under-reporting occurred more frequently than would be expected due solely to chance. Consequently, it may be prudent to regard measures of agreement for the diseases with evidence of differential misclassification with somewhat more caution compared to the diseases for which the exact binomial test failed to reject the null hypothesis that any misclassification was nondifferential.

To address Specific Aims II and III, multivariable logistic regression modeling was performed. Sub Aim 1 for both Aims examined the effect of survival time as well as age at diagnosis, gender, diagnosis era, ICD revision in use at time of death, and race on the odds of agreement between UCOD and ICR site code. Sub Aim 2 for both Aims evaluated the odds of agreement between ACC and site code given the same set of possible predictors. The outcome of interest in both models was the odds ratio of correctly matching DC information to cancer incidence data from the ICR.

Multivariate logistic regression modeling indicated that survival time after cancer diagnosis and age at diagnosis were significant predictors of the odds of agreement between the UCOD or ACC and the cancer incidence site code recorded by the ICR. As expected, both regression models indicated that greater survival time after cancer diagnosis decreased the odds of agreement between DC data and cancer incidence site code. Age at diagnosis turned out to have varying effects on the odds of agreement, with membership in either of the younger quartiles of age at diagnosis (22-60 or 61-68 years) compared to the oldest quartile (75 or more years) being additive factors in both models. Membership in the third category of age at diagnosis (69-74 years) compared to the oldest category was a negative factor in both models to predict the odds of agreement between DC data and cancer incidence data recorded by the ICR. For UCOD, gender and diagnostic era improved the fit of the model, despite the fact that they were not significant predictors on their own. The fit of the ACC model to the data was improved by addition of gender and a quadratic term on survival time after cancer diagnosis.

As expected, odds ratios of agreement between both the UCOD and ACC on DCs decreased with increasing time of survival after cancer diagnosis. Additionally, workers whose age at diagnosis was less than or equal to the median for the cohort had increased odds of agreement between DC and cancer incidence data compared to workers diagnosed at ages greater than the median. Finally, male workers were found to have lower odds of agreement between DC and ICR incidence data compared to females. Workers with shorter survival, younger age, and female gender all were found to have increased odds of agreement compared to their counterparts.

Similar to results presented by Demers et al. (1992), our findings indicated that DCs underestimated cancer incidence. Rather than focus on specific cancers with varying mortality rates, we evaluated survival time for all workers. We found survival time to be a main effect in the logistic regression models to estimate the odds of agreement between UCOD or ACC and the ICR data.

As stated previously, Freedman et al. (2006) reported under-ascertainment of cancers identified by DCs compared to registry data. Our study also found that DCs under-report cancer incidence compared to the ICR data. Two occupational studies, Cottrell et al. (1992) and Davis et al. (1992), reported better disease surveillance results using manual review of DCs to ascertain any mention of the disease of interest. Sensitivity of ACC relative to the site of the first incident primary cancer reported by the ICR were equal to or higher than corresponding measures for UCOD for all of the cancers included in this study. However, this was a function of the methodology used.

The findings of this research supports the views of previous authors (Boyle 1989; Feinstein & Esdaile 1987), who discussed the limitations of using DCs for ascertainment of cancer incidence data. The findings are also in agreement with other researchers (Demers et al., 1992; Pickle et al., 2007) who found that longer survival time is a negative predictor of agreement between DC data and SEER registry incidence data.

Results of this study should be generalizable to other occupational cohorts in similar workplaces during similar time frames. Measures of agreement between DC data and cancer incidence data indicate that, particularly in areas not covered by population-based cancer registries, DCs can serve as reasonable predictors of cancer incidence for certain diseases, especially rapidly fatal cancers. In addition, survival time and age at

diagnosis were found to be significant predictors of agreement between DC and cancer incidence data. Both UCOD and ACC differentially misclassified some cancers more than would be expected due to chance alone. Measures of agreement for the diseases with evidence of differential misclassification should be regarded with somewhat more caution compared to the diseases for which the exact binomial test failed to reject the null hypothesis that any misclassification was nondifferential. Differential misclassification can cause bias measures of association either toward or away from the null, either over or under-estimating the strength of the association. Additionally, findings for diseases with small sample sizes should be interpreted carefully. Measures of agreement for such diseases are difficult to estimate accurately.

Limitations

This study has a number of limitations. While the sample size provided large enough numbers of workers diagnosed with relatively more common cancers, we were limited in our ability to evaluate several less frequently occurring cancers. For example, there were only five incident cases of testicular cancer recorded by the ICR. For this disease, there was insufficient power to reject the null hypothesis of no differential misclassification, despite the fact that both the UCOD and ACC under-reported every case of testicular cancer among the IAAAP worker cohort.

This research was also conducted with the assumption that the DC and ICR data used were coded correctly in accordance with ICD guidelines. To keep the number of disease categories manageable while having enough study subjects to analyze, ICD site codes were categorized at the three digit level. This created its own set of problems because not all disease categories are equivalent at the three digit level across ICD

revisions 8-10 as well as ICD-O-3. Particularly problematic in this respect was Non-Hodgkin Lymphoma, one of the 10 most common cancers. Other less common cancers that were not evaluated separately included leukemia, myeloma, other lymphoma, cancers of the oral cavity and pharynx, gallbladder, bones and joints, soft tissue including heart, miscellaneous cancers, and several other miscellaneous categories within assorted organ systems. Morphology codes were not evaluated, except that the sixth digit was ascertained to identify invasive neoplasms for inclusion and *in situ* tumors for exclusion. This made it impossible to differentiate cancers with overlapping site codes, such as many of the cancers of the oral cavity and pharynx with Non-Hodgkin Lymphoma.

Other limitations of this study included our inability to evaluate multiple primary cancers and to better evaluate the effects of multiple CODs and associated conditions listed on the DC. Approximately one in six cancer patients is affected by multiple primaries (Grouse, 2006). It is thought that the mortality experience for this sizable segment of the population afflicted with cancer may be significantly different compared to other cancer patients. Future work includes assessing subjects with multiple primaries as well as developing methods to take better advantage of all of the data included among ACC on DCs.

Further, it is uncertain whether these results are generalizable to other states. We were also unable to examine socio-economic status (SES) of the study subjects, since educational status that can be used as a surrogate indicator of SES was only added to the U.S. Standard Certificate of Death with the 1989 revision (Hetzel, 1997) Finally, since differences exist in the level of training required of various types of certifiers (attending physician or medical examiner compared to deputy coroner,) we originally intended to

evaluate the potential effects of different certifiers of death on the odds of agreement between DC and ICR data. Unfortunately this information was found to be inconsistently reported across the different versions of the DC.

Strengths

This study also had many strengths. Primary among them was the overall high quality of the data from the ICR, a population-based SEER cancer registry which has operated in Iowa since 1973. This study also took advantage of more of the information available on the DC by evaluating the ability of not only the UCOD to reflect cancer incidence, but ACC as well. The purpose of this element of the study design was to attempt to assess more of the total burden of cancer by capturing non-fatal disease as well as mortality information. This research also benefited from a reasonably large sample size and while the 33-year time frame did present some challenges, it also provided a good deal of follow-up time for diseases to manifest within the cohort.

Future Research

Workers with multiple primary malignant neoplasms were excluded from this study. We would like to be able to evaluate this important subset of the population in future research. This approach eliminated approximately 15.3% of the cohort. A subject-based approach to evaluate these excluded neoplasms could be part of a future study design.

Additionally, even if more than one cancer was listed on the DC, we were only able to estimate measures of agreement for the condition which matched the ICR site code. Therefore, future work includes development of methods to more fully evaluate the

utility of using this source of data as a predictor of cancer incidence in the absence of more comprehensive information.

CONCLUSION

Our findings indicate that DCs can be useful for predicting cancer incidence for some types of cancer. The UCOD correctly reflected 75% or more of the incident cancers identified by the ICR for esophageal, liver and IBD, pancreatic, lung and bronchus, ovary and other uterine adnexa, and brain and ONS neoplasms. When ACC were considered, sensitivities relative to ICR cancer incidence data rose to 80% or greater for the same six diseases. PV+s of the UCOD for these six diseases were all 80% or greater, indicating that 80% or more of the workers with one of these cancers listed as the UCOD also had that disease identified as a first primary malignancy by the ICR.

Study results also showed that DCs were less helpful for predicting cancer incidence among other cancer types (stomach, colon and rectum, larynx, skin melanoma and other MN, breast, cervix uteri, corpus and uterus NOS, prostate, testis, urinary bladder, kidney and renal pelvis, and thyroid). Four of the six cancers for which the UCOD demonstrated sensitivity greater than 75% relative to the ICR incidence data (esophageal, liver and IBD, ovary and other uterine adnexa, and brain and ONS) showed no evidence of differential misclassification, indicating that using DCs to predict cancer incidence misclassified the occurrence of first malignant primary neoplasms no more frequently than would be expected due to chance alone. The other two diseases, cancers of the pancreas as well as lung and bronchus, showed evidence of differential misclassification indicating that measures of association for these diseases may be over or under-estimated. Results for ACC were very similar.

Survival time after cancer diagnosis was found to be an important predictor of the odds of agreement between either the UCOD or ACC and cancer incidence data reported

by the ICR. Both the UCOD and ACC were found to have higher estimates of the odds of agreement with the ICR cancer incidence data for workers with shorter survival times after cancer diagnosis. Age at cancer diagnosis was also found to be an important predictor of agreement between DC data and ICR-reported cancer occurrence for both the UCOD as well as ACC.

This research demonstrates that DCs can be useful predictors of cancer occurrence for certain diseases, especially among worker populations and in areas or during time frames not covered by population-based cancer registries. Assuming the findings of this paper are generalizable to other worker cohorts, the reported PV+ and sensitivity for the various cancer types may be useful for estimating the degree of under-reporting of DC cancer information in other studies that rely on DCs to reconstruct cancer incidence. However, these findings are most generalizable to past worker cohorts in the upper Midwest. Similar studies are required in other areas of the United States to further assess the representativeness of our findings.

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