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探討半導體產業癌症及先天缺陷發生之風險

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Exploring Risks for Reproductive Health and Cancer in Semiconductor Workers

Abstract

Problem: A retrospective cohort mortality and morbidity study was conducted to investigate the possible association between occupational exposure in semiconductor industry and cancer.

Methods: We obtained information of eight companies workers in the semiconductor cohort from the Bureau of Labor Insurance in Taiwan. Workers with cancer were identified after linking with databases of death and cancer registration from the Department of Health of Taiwan. The NIOSH life table analysis system was used to generate person-years-at-risk and the expected numbers of death for 94 categories of death, using Taiwan referent rates.

Results: A total of 19,816 male and 27,610 female workers had been employed during 1980-2000. From data linkage, we found 136 cancer cases and 60 cancer deaths. All malignant neoplasms were also less than expected, indicating a possible healthy worker effect. But there were slight increases of standardized mortality ratios and incidence ratios for cancers of nasopharynx, ovary, and leukemia with 95% confidence interval including 1.

Conclusions: Given that workers are generally still young, we recommend that the cohort need to be followed longer in the future.

Key words: standardized mortality ratios, standardized incidence ratios, cancer, semiconductor manufacture, Taiwan

Introduction

There are three categories in the semiconductor industry in Taiwan, and we're going to aim at the design and manufacturing of semiconductor devices. Large quantities of potent gases, dopants, photoactive chemicals (photoresists, photoinitiators), solvents, and ionizing radiation are used in the semiconductor manufacturing process,¹⁻⁴ but is uncertain about the occurrence of cancer from exposures in this industry.

Previous research on cancer risks of working in the semiconductor industry is limited and has produced conflicting results.⁵⁻⁷ The aim of this study was to determine the cancer incidence and mortality of semiconductor workers in Taiwan, to evaluate suspected cancers and potential carcinogens in the semiconductor industry. It is worthy that to follow up the concerns that had been expressed, and to assess the need for further investigation.

Population and Methods

The original cohort consisted of 19,816 male and 27,610 female workers from eight semiconductor companies in the Hsinchu Science-based Industrial Park (HSIP) which locates in the northwest of Taiwan. To be eligible for this cohort, workers in eight companies must be employed for a period of at least six months during the period 19 August 1980 to 21 June 2000. The identification (ID) numbers of cohort members were collected from the Bureau of Labor Insurance (BLI), and demographic data of date of birth, gender, and dates of new and change of employment, and retirement were retrieved. Then, each personal ID was linked with both the datasets of National Mortality Registry (NMR) and cancer registry (NCR) from the Department of Health (DOH) of Taiwan.

The NMR has maintained a computerized file of all death certificates issued in Taiwan from 1980 to 2003. The underlying cause of death has been systematically coded according to the ninth revision of the International Classification of Diseases (ICD9). The NCR was

established by record linkage of cancer registries 1980 through 2001, including identification number, dates of birth and death, places of living, codes of education and village, and ICD code. The cause of cancer was coded from the cancer registry by using the International Classification of Diseases for oncology (ICD-O). We included the following categories of neoplasm (ICD-9 code 140-239; ICD-O code 140-199; 981-984) as outcomes in our analyses. A total of 60 cancer deaths and 136 of cohort members occurred during the follow up period, with a successful follow-up rate of 100%.

Age, sex, and calendar-time- specific standardized mortality ratios (SMRs) and incidence ratios (SIRs) were derived from the modified life table analysis system (LTAS) developed by NIOSH^{8,9} to calculate person-years at risk (PYAR) and the expected number of deaths, using of general population in Taiwan. For each worker in our study, the period of observation started after 6 months of employment in eight semiconductor companies, whichever was later, and ended at date of death, or December 31, 2003, whichever was earlier. In addition, person-years were stratified by gender, duration of employment, calendar year and company. All analyses were done using the PC version of the LTAS¹⁰ [<http://www.cdc.gov/niosh/ltindex.html>]. We calculated the total number of deaths or cancers observed, and the SMR or SIR, and the 95% confidence interval (two sided) for both. To calculate the dose response relationship, we divided the workers into three groups based on the duration of employment, that is, employment of less than or equal to 4 years, longer than 4 year but less than or equal to 10 years, and longer than 10 years. Length of employment analysis was carried out for cancer sites with a minimum of three deaths (data not shown). The dose-response relationship of period effect was also estimated. We divided the workers into four groups based on four time intervals: 1980-1989, 1990-1994, 1995-1999, and 2000-2003 (data not shown).

Results

A total of 19,816 men and 27,610 female workers contributing men 136,718.6 and female 198,383.7 person-years were included in the study. Table 1 presents the distribution of the cohort by job change, age of first employment, age of study end, the first year of employment, duration of employment, vital status, cancers, and company. 25.3% male and 48.7% female workers came from Hsinchu county, and other workers came from different countries and cities. The duration of employment of the cohort is relatively short with a median of 3.1 (range 0.5–19.8) years. 89.6% of the cohort was first employed later than 1990. 67.1% of the cohort was 20-29 year old at first employment, and 90.2% of the cohort was 20-39 year old at study end. The median time since first employment, based on employment in the eight semiconductor companies while they were operating, is 6 years. Almost all of the workers and person-years were from design and manufacturing of semiconductor devices or chips. Of the 13944 (26%) workers who had been employed at A1 company, 2348 (4.4%) had been employed at H8 company, and other workers had been employed at other six companies. But one worker maybe had serviced more than two companies in the eight semiconductor companies.

Table 2 shows the results of the analysis for all causes of death, and mortality from all causes was less than expected. Mortality from all malignant neoplasms was also less than expected. Among the outcomes of a priori interest, non-significant increases in mortality from nasopharynx cancer, ovary cancer, and leukemia were observed. Within the major category of non-malignant neoplasm, mortality from other circulatory system, skin, and violence were non-significantly increased.

Table 3 shows the results of the analysis for all causes of cancers, and morbidity from all

cancer was less than expected. Among the outcomes of a priori interest, non-significant increases in cancer morbidity from oral cavity, nasopharynx, other respiratory system, ovary, testes, other skin, connective tissue, and leukemia.

Discussion

We did not find any significant high risk for either the mortality or incidence of each cancer. There also was an obviously healthy worker effect in the semiconductor industry. (Table 2 and 3) However, we point out the possibility of cancers with potential carcinogens in this industry that justifies further investigation.

The observed numbers of all-cause death in males and in females were not significantly lower than the expected, and the observed numbers of cancers also were not significantly elevated. Firstly, these results could have been influenced with the small number of each cancer. It, however, is the best of our ability that the cohort was as complete as possible. A total of 47,426 workers in eight companies were completely collected from BLI,¹¹ and members of the cohort were more than those in the past studies⁵⁻⁷ of the semiconductor industry. The cohort is shorter follow-up time, because the semiconductor industry was established for twenty years ago. Secondly, because we focused on the design and manufacturing of semiconductor devices only those processes were unique, Thirdly, cancer death and registration from DOH were complete¹² and accurate,¹³ due to the compulsory requirement by laws in Taiwan. The data of mortality or incidence rate in Taiwan was used in many mortality or morbidity studies,¹¹⁻¹⁵ they had been verified in the past. However, we must take consideration into account of a healthy worker effect.

The healthy worker effect has been attributed to healthy individuals being selected for employment.^{16,17} The discovery of a healthy worker effect was based on mortality studies, so that the proposition that occupational cohorts have lower disease incidence than the general population is speculative, and can only be clarified by concurrent analyses of disease incidence and mortality.⁵⁻⁷ A reduced overall mortality for all cause deaths and morbidity for all cancer risks compared to the general population was also observed in our study, which was generally recognized as the so called healthy workers effect. The prevalence of tobacco smoking was 47.7% among male workers, and 5.9% among female workers in Taiwan.¹⁸ Approximately 9.3% of the female workers were smoking at the time of the survey.¹⁹ Smoking rate of female workers in the semiconductor industry was higher than female workers in Taiwan. Thus, a plausible explanation of the healthy worker effect, at least in the case of cancer, may be the selective employment of healthy workers from the source population (healthy hire effect).

Large quantities of potent gases, dopants, photoactive chemicals (photoresists, photoinitiators), solvents, and ionizing radiation are used in the semiconductor manufacturing process, but is uncertain about the occurrence of cancer from exposures in this industry. The toxic materials¹ needed to make the wafer are staggering in amount and include highly corrosive hydrochloric acid; metals such as arsenic, cadmium, and lead; volatile solvents such as methyl chloroform, toluene, benzene, acetone, and trichloroethylene; and toxic gases such as arsine. Many of these chemicals are known or probable human carcinogens in the International Agency for Research on Cancer (IARC). The list of carcinogen group 1 included gallium, arsenic, beryllium, cadmium, benzene, ethylene oxide, benzedrine, and sulphuric acid mist^{1,22}. Many by-products in the semiconductor manufacturing maybe were carcinogens, they were worthy to be explored.

Only few attempts had so far been made at cancers in the semiconductor industry. Although

two cohort studies⁵⁻⁷ had been followed up for more than 20 years, there is little consistency as to cancer mortality and morbidity in the semiconductor industry. Although we don't know the cause of these discrepancies, it is worthy to mention any possible cancer related to the potential carcinogens. That is the occurrence of cancers equal to three or more cases and their SMR or SIR more than one in the two previous and our studies. Thus, digestive [150-158], respiratory [160-163], skin [172-173], and lymphatic and haematopoietic [200-208] were worthy to further discussion. Although a few cancer cases were observed, there was no cancer cluster in this study.

The limitations of cohort studies in the semiconductor industry in past were as follows. First, the follow-up time may be too short observe occupationally-related cancers. In addition, there was no information on exposure levels to carcinogens in the semiconductor companies. Moreover, those studies did not control for potential confounders, such as smoking, drinking, reproductive history, and dietary habits.

Nasopharynx, ovary, and testis cancers were found to have a potential risk in this study. The excess risk of the above-mentioned cancers was found in semiconductor studies. We had to identify those results, avoid overstatement, and findings must be interpreted more cautiously. There remains the possibility that some of this excess may be related to work at the companies. It is inevitable that the workers are much younger whose average age is less than 50 years old and are not senior enough in the limitations of this study.

The confounders in exposure assessment and healthy worker effect caused lower evaluation of the effects in cancer risks in the semiconductor industry. So far, it is concluded that this study provided no evidence that occupational exposure in semiconductor industry was associated with human cancer risk. Therefore, it needs to follow up in the future.

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Table 1. The Characteristics for both male and female workers in the eight semiconductor companies

Characteristics	Male	Female
	N (%)	N (%)
Company (date at the beginning) N ^a (personal years)	N ^a (personal years)	N ^a (personal years)
A1 (1980)	5807 (40789.4)	8137 (61623.8)
B2 (1987)	4356 (26905.4)	8139 (48452.9)
C3 (1987)	3491 (23053.0)	4913 (35939.8)
D4 (1988)	3015 (17290.8)	3209 (18725.9)
E5 (1990)	1681 (11451.7)	2016 (13026.6)
F6 (1994)	1622 (8062.2)	1928 (9720.0)
G7 (1991)	1281 (5580.2)	1759 (7524.7)
H8 (1994)	1110 (3585.9)	1238 (3370.0)
Job change		
1	17534 (88.5)	24472 (88.6)
2	2032 (10.3)	2666 (9.7)
3+	250 (1.3)	472 (1.7)
Age at first employment		
<20	245 (1.2)	8187 (29.7)
20-29	15038 (75.9)	16769 (60.7)
30-39	3997 (20.2)	2525 (9.1)
40-49	472 (2.4)	117 (0.4)
50+	64 (0.3)	12 (0.0)
Age at end of study		
<20	5 (0.0)	109 (0.4)
20-29	4672 (23.6)	15900 (57.6)
30-39	12090 (61.0)	10116 (36.7)
40-49	2686 (13.6)	1396 (5.1)
50+	363 (1.8)	89 (0.3)
First year of employment		
1980-1984	407 (2.1)	876 (3.2)
1985-1989	1663 (8.4)	1985 (7.2)
1990-1994	4764 (24.0)	7370 (26.7)
1995-1999	11546 (58.3)	14619 (52.9)
2000	1436 (7.2)	2760 (10.0)
Duration of employment (years)		
<5	15488 (78.2)	22573 (81.8)
5-9	3437 (17.3)	4075 (14.8)
10+	891 (4.5)	962 (3.5)
Vital Status		
Alive	19749 (99.7)	27538 (99.7)
Dead	67 (0.3)	72 (0.3)
Cancers		
No	19758 (99.7)	27521 (99.7)
Yes	58 (0.3)	89 (0.3)
Total	19816 (100)	27610 (100)

^a one worker maybe had serviced more than two companies in the eight semiconductor companies.

Table 2. Observed and expected numbers of deaths for standardized mortality ratio (SMR) stratified by cause and gender in the eight semiconductor manufacturing companies^a

Cause	ICD-9	Male			Female		
		O ^b	E ^b	SMR (95%CI) ^c	O ^b	E ^b	SMR (95%CI) ^c
All Deaths	1-999	98	361.89	0.27 (0.22-0.33)**	93	148.00	0.63 (0.51-0.77)**
All Cancers	140-209	27	65.51	0.41 (0.27-0.60)**	23	33.91	0.68 (0.42-1.02)
nasopharynx	147	5	4.50	1.11 (0.36-2.60)	2	1.21	1.65 (0.20-5.96)
stomach	151	2	3.22	0.62 (0.08-2.25)	-	2.65	-
colon and rectum	153, 154	3	4.70	0.64 (0.13-1.87)	2	3.47	0.58 (0.07-2.08)
liver and intrahepatic bile ducts	155	5	20.68	0.24 (0.08-0.56)**	3	2.55	1.17 (0.24-3.43)
gall bladder and extrahepatic bile ducts	156	-	0.72	-	1	0.40	2.53 (0.06-14.06)
trachea, bronchus, and lung	162	1	6.04	0.17 (0.00-0.92)*	2	2.83	0.71 (0.09-2.55)
other parts of respiratory system	160, 163-165	1	0.41	2.43 (0.06-13.50)	-	0.24	-
breast	174, 175	-	0.02	-	3	6.21	0.48 (0.10-1.97)
cervix uteri		-	0.00	-	1	2.82	0.35 (0.01-1.97)
ovary, fallopian tube, and broad ligament	183	-	0.00	-	2	1.37	1.46 (0.18-5.26)
Melanoma	172	-	0.20	-	1	0.15	6.87 (0.17-38.19)
brain	191	1	1.78	0.56 (0.01-3.12)	-	1.35	-
thyroid gland	193	0	0.10	-	1	0.10	9.82 (0.25-54.57)
connective tissue	171	1	0.46	2.16 (0.05-11.99)	-	0.29	-
other and unspecified sites	187, 194-199	-	1.27	-	1	0.86	1.17 (0.03-6.49)
Non-Hodgkin's lymphoma	200, 202	-	2.39	-	2	1.76	1.14 (0.14-4.10)
Leukemia and aleukemia	204-208	7	3.21	2.18 (0.87-4.49)	2	3.07	0.65 (0.08-2.35)
Myeloma	203	1	0.21	4.73 (0.12-26.25)	-	0.10	-
Diabetes mellitus	250	-	6.74	-	1	2.25	0.44 (0.01-2.47)
Nervous system and sense organs	320-389	-	4.91	-	1	3.58	0.28 (0.01-1.55)
Heart	390-398, 402, 404, 410-414, 420-429	8	18.28	0.44 (0.19-0.86)*	1	5.11	0.20 (0.00-1.09)
Other circulatory system	400, 401, 403, 405, 415-417, 430-459	3	18.14	0.17 (0.03-0.48)**	9	5.98	1.50 (0.69-2.86)
Respiratory system	460-519	2	8.88	0.23 (0.03-0.81)*	1	3.89	0.26 (0.01-1.43)

Digestive system	520-579	6	45.53	0.13 (0.05-0.29)**	2	5.56	0.36 (0.04-1.30)
Genitourinary system	580-629	-	4.12	-	2	2.55	0.79 (0.10-2.84)
Skin and subcutaneous tissue	680-709	-	0.80	-	4	2.43	1.65 (0.45-4.22)
Symptoms, signs and ill-defined conditions	780-796, 798, 799	2	21.73	0.09 (0.01-0.33)**	4	8.61	0.46 (0.13-1.19)
Accidents	E800-E949	34	112.32	0.30 (0.21-0.43)**	23	41.47	0.55 (0.35-0.83)**
Violence	E950-E978	12	31.62	0.38 (0.20-0.66)**	18	17.64	1.02 (0.60-1.61)
HIV-related	042-044	1	1.36	0.74 (0.02-4.10)	-	0.13	-
Other causes	001-009, 020-139, 240-246, 251-279, 630-678, 740-779, 794, 797, E980-E999, and blank	3	12.85	0.23 (0.05-0.68)**	4	9.20	0.43 (0.12-1.11)

a Person-years at risk and observed deaths began accruing in 1980 for the analysis based on rates for Taiwan.

b O, observed; E, expected. ; c SMR, standardized mortality ratio, 95% CI, 95% confidence interval.

* Two-sided Poisson, p , 0.05. ** Two-sided Poisson, p , 0.01.

Table 3. Observed and expected numbers of malignant neoplasms (Mn) for standardized incidence ratio (SIR) stratified by cause and gender in the eight semiconductor manufacturing companies^a

Cause	ICD-O	Male			Female		
		O ^b	E ^b	SIR (95%CI) ^c	O ^b	E ^b	SIR (95%CI) ^c
All Cancers	140-199, 980, 981-984	51	84.76	0.60 (0.45-0.79)**	85	114.56	0.74 (0.59-0.92)**
oral cavity	140, 141, 143-146, 148, 149	1	14.66	0.07 (0.00-0.38)**	2	1.09	1.83 (0.22-6.60)
major salivary glands	142	1	0.45	2.25 (0.06-12.49)	-	0.49	-
Nasopharynx	147	9	8.20	1.10 (0.50-2.08)	4	3.05	1.31 (0.36-3.35)
Stomach	151	3	4.13	0.73 (0.15-2.12)	2	3.14	0.64 (0.08-2.30)
small intestine	152	1	0.41	2.41 (0.06-13.41)	-	0.22	-
colon and rectum	153, 154	6	7.97	0.70 (0.27-1.64)	3	5.95	0.50 (0.10-1.47)
liver and intrahepatic bile ducts	155	8	18.15	0.44 (0.19-0.87)*	3	2.68	1.12 (0.23-3.28)
Pancreas	157	-	0.87		1	0.29	3.43 (0.09-19.05)
trachea, bronchus, and lung	162	2	4.76	0.42 (0.05-1.52)	1	2.25	0.45 (0.01-2.47)

other parts of respiratory system	160, 163-165	3	1.27	2.37 (0.49-6.92)	-	0.84	-
Breast	174, 175	-	0.07	-	16	22.46	0.71 (0.41-1.16)
cervix uteri	179, 180	-	0.00	-	22	36.02	0.61 (0.38-0.92)*
ovary, fallopian tube, and broad ligament	183	-	0.00	-	8	5.64	1.42 (0.61-2.80)
Testes	186	3	1.19	2.53 (0.52-7.40)	-	0	-
kidney and other urinary organs	189	1	1.37	0.73 (0.02-4.07)	-	0.76	-
Bladder	188	1	1.67	0.60 (0.02-3.32)	1	0.38	2.62 (0.07-14.58)
Other skin	173	2	2.16	0.93 (0.11-3.35)	3	2.35	1.28 (0.26-3.73)
Brain	191	1	2.44	0.41 (0.01-2.27)	-	2.25	-
thyroid gland	193	-	2.21	-	13	12.27	1.06 (0.56-1.81)
connective tissue	171	2	1.30	1.54 (0.19-5.57)	-	1.38	-
other and unspecified sites	187, 194-199	1	3.85	0.26 (0.01-1.44)	4	2.96	1.35 (0.37 -3.46)
Leukemia and aleukemia	169, 980, 981-984	6	3.27	1.84 (0.67-4.00)	2	3.40	0.59 (0.07-2.13)

a Person-years at risk and observed cancers began accruing in 1980 for the analysis based on rates for Taiwan.

b O, observed; E, expected.

c SIR, standardized incidence ratio, 95% CI, 95% confidence interval.

* Two-sided Poisson, p , 0.05.

** Two-sided Poisson, p , 0.01.