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Original Article

Cancer Mortality and Incidence in Korean Semiconductor Workers

Hye-Eun LEE, Eun-A KIM, Jungsun PARK and Seong-Kyu KANG

Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency, Incheon, Korea

Objectives: The purpose of this study was to evaluate cancer risks in the Korean semiconductor industry.
Methods: A retrospective cohort study was performed in eight semiconductor factories between 1998 and 2008. The number of subjects was 113,443 for mortality and 108,443 for incidence. Standardized mortality ratios (SMR) and standardized incidence ratios (SIR) were calculated.
Results: The SMR of leukemia was 0.39 (95% Confidence Interval 0.08-1.14) in males (2 cases) and 1.37 (0.55-2.81) in females (7 cases). The SMR of non-Hodgkin's lymphoma (NHL) was 1.33 (0.43-3.09, 5 cases) in males and 2.5 (0.68-6.40, 4 cases) in females. The SIR of leukemia was 0.69 (0.30-1.37, 8 cases) in males and 1.28 (0.61-2.36, 10 cases) in females. The SIR of NHL in females was 2.31 (1.23-3.95, 13 cases) and that of thyroid cancer in males was 2.11 (1.49-2.89, 38 cases). The excess incidence of NHL was significant in female assembly operators [SIR=3.15 (1.02-7.36, 5 cases)], but not significant in fabrication workers. The SIR of NHL in the group working for 1-5 years was higher than the SIR of NHL for those working for more than five years. The excess incidence of male thyroid cancer was observed in both office and manufacturing workers.
Conclusion: There was no significant increase of leukemia in the Korean semiconductor industry. However, the incidence of NHL in females and thyroid cancer in males were significantly increased even though there was no definite association between work and those diseases in subgroup analysis according to work duration. This result should be interpreted cautiously, because the majority of the cohort was young and the number of cases was small.

Key Words: Semiconductors, Leukemia, Lymphoma, Cancer, Cohort studies

Introduction

Concern that there might be leukemia clusters in a semiconductor company in Korea was first expressed in 2007 [1] by a workers' support group and this was covered in the media. The Occupational Safety and Health Research Institute (OSHRI) of the Korea Occupational Safety and Health Agency (KOSHA) conducted an environmental assessment of the semiconductor company in 2008 in order to determine whether Group 1 occupational carcinogens based on the international agency for research on cancer (IARC), such as benzene and ionizing radiation, were related with malignant lymphohematopoietic (LHP) cancers. Known occupational carcinogens were not found at the workplace, and benzene was below the detection limit (1 ppb) and ionizing radiation was similar to the natural background level [1,2]. However, another worker, who had worked with the first case, subsequently died from leukemia. From 2007 to 2010, OSHRI investigated seven cases of malignant LHP disorders to evaluate work-relatedness in the semiconductor industry, which were requested by the Korea Workers' Compensation and Welfare Service (COMWEL) [1]. Considering subsequent LHP cancer cases, the Epidemiological Investigation Review Board of OSHRI recommended that

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Correspondence to: Eun-A KIM
Occupational Safety and Health Research Institute
Korea Occupational Safety and Health Agency
478, Munemi-ro, Bupyong-gu, Incheon 403-711, Korea
Tel: +82-32-510-0829, **Fax:** +82-32-518-0862
E-mail: toxneuro@kosha.net

a nationwide epidemiological investigation was necessary to evaluate the risk of LHP cancer in the semiconductor industry. A nationwide epidemiological investigation by OSHRI was conducted in 2008.

There were similar cases in the U.S. firm IBM and the National Semiconductor in the UK. In 1985, a chemist working in the IBM research facility in San Jose, California, revealed that there was a cluster of cancers in his colleagues [3]. In 1996, 128 former IBM workers and their families, including 11 deceased workers by cancer, sued the chemical suppliers insisting they had suffered adverse health effects, including cancers and miscarriages, from work exposure to hazardous chemicals [4]. In 1998, concerns about a suspicious cluster of cancers in the Greenock Plant of National Semiconductor Limited in the UK was expressed in the form of workers' support group actions, media coverage, and parliamentary activity [5]. In response to these issues of semiconductor workers' cancers, epidemiological studies were performed, but a definitive association between work in semiconductor manufacturing and cancers was not found [5-8]. Aside from studies targeting these workforces, there were some others exploring cancer risk in the semiconductor industry, but they have not provided consistent evidence that exposures in the industry were associated with cancer [9-11].

The aim of this study was to determine the incidence and mortality rates of cancers in Korean semiconductor workers in order to evaluate the association between cancers and work in the industry.

Materials and Methods

Cohort definition

Subjects were current and former workers of eight factories and each factory belonged to one of five semiconductor manufacturers from the members of the Korea Semiconductor Industry Association (KSIA). KSIA included 9 semiconductor device manufacturers and many other related companies, for example parts making, semiconductor architecture, and semiconductor equipment. The five companies selected to participate in the study comprised all of the semiconductor manufacturers in Korea that performed fabrication processes. The semiconductor manufacturing process is generally composed of fabrication and assembly. Fabrication processes were composed of the following six steps: diffusion, lithography, etching, ion implantation, chemical vapor deposition (CVD), and metallization [2]. Four factories were fabrication facilities, one was for assembly and three factories had both fabrication and assembly processes. These 8 factories were all the factories of the 5 manufacturers except the factories outside Korea.

The cohort included workers who had worked at any of the eight factories for more than one day between 1998 and the last year of the study (2008 for mortality, 2007 for incidence analysis), and who had a record containing information on birth date, gender, resident registration number (personal identification number), hiring date, job description, and department. Follow-up for workers was started in 1998 because worker personnel records were available from 1998 in all factories although most of the factories were established before 1998. One of the factories was opened in 1999, 2 of them were opened in 1997, and the others were established in the 1970's or 1980's. The last year of the cohort for mortality rates was 2008, which was when death certificate data were available, while that for incidence rates was 2007 when the cancer registry data were available. Individual exposure data were not available, but workers in the same subgroups were assumed to have the same exposures. There were some industrial hygiene monitoring data, but it was based on specific places and processes, like Oxidation, Lithography, and so on. These data could not be linked with workers personal data because there was no information regarding working place or detailed process.

Cohorts were first classified into office and manufacturing workers, and then manufacturing workers were divided into operators, engineers (process engineers and service engineers), supervisors, and utility workers. Operators and engineers were the main workers working in the clean-room. Operators typically handle manufacturing equipment, and service engineers maintain the manufacturing equipment. Process engineers improve the process stream by programming. Supervisors are close to office workers but they occasionally go in the clean-room. Utility workers are not directly involved in the manufacturing process, but they maintain general utilities for facilities outside the clean-room, like electricity and gas supply. Workers who had worked at any time in the manufacturing process were classified as manufacturing workers, while workers that had never worked in the manufacturing process were classified as office workers. Among manufacturing workers, employees that had worked in two or more jobs were assigned as workers in those jobs, too. Consequently, a worker who changed from operator to engineer or vice versa was assigned to both job categories. Manufacturing workers were categorized to fabrication or assembly according to their experience of having ever worked in those processes. Also, workers who had work history in both fabrication and assembly were categorized to both processes. Grouping of cohorts was performed in consultation with the Human Resource Teams and the Occupational Health Departments of surveyed manufacturers.

Table 1. Number of subjects by selected characteristics for mortality and incidence analysis

		Mortality cohort			Incidence cohort		
		Male n (%)	Female n (%)	Total n (%)	Male n (%)	Female n (%)	Total n (%)
Total*		48,589 (100.0)	64,854 (100.0)	113,443 (100.0)	46,826 (100)	62,107 (100)	108,933 (100)
Birth year	< 1940	22 (0.0)	2 (0.0)	24 (0.0)	22 (0.0)	2 (0.0)	24 (0.0)
	1940-1949	266 (0.5)	52 (0.1)	318 (0.3)	258 (0.6)	52 (0.1)	310 (0.3)
	1950-1959	1,963 (4.0)	89 (0.1)	2,052 (1.8)	1,941 (4.1)	89 (0.1)	2,030 (1.9)
	1960-1969	12,033 (24.8)	341 (0.5)	12,374 (10.9)	11,999 (25.6)	339 (0.5)	12,338 (11.3)
	1970-1979	25,271 (52.0)	20,114 (31.0)	45,385 (40.0)	24,858 (53.1)	20,068 (32.3)	44,926 (41.2)
	1980-1989	9,024 (18.6)	43,652 (67.3)	52,676 (46.4)	7,748 (16.5)	41,429 (66.7)	49,177 (45.1)
	≥ 1990	10 (0.0)	604 (0.9)	614 (0.5)	0 (0.0)	128 (0.2)	128 (0.1)
Job	Office workers	11,350 (23.4)	3,889 (6.0)	15,239 (13.4)	10,759 (23)	3,735 (6)	14,494 (13.3)
	Manufacturing workers	37,234 (76.6)	60,965 (94.0)	98,199 (86.6)	36,062 (77)	58,372 (94)	94,434 (86.7)
Hire date	< 1991	9,222 (19.0)	1,353 (2.1)	10,575 (9.3)	9,208 (19.7)	1,352 (2.2)	10,560 (9.7)
	1992-1997	15,218 (31.3)	17,209 (26.5)	32,427 (28.6)	15,210 (32.5)	17,204 (27.7)	32,414 (29.8)
	1998-2003	10,245 (21.1)	22,723 (35)	32,968 (29.1)	10,239 (21.9)	22,717 (36.6)	32,956 (30.3)
	≥ 2004	13,904 (28.6)	23,569 (36.3)	37,473 (33.0)	12,169 (26)	20,834 (33.5)	33,003 (30.3)
Years worked	Unknown	2 (0.0)	10 (0.0)	12 (0.0)	66 (0.1)	775 (1.2)	841 (0.8)
	< 1 month	134 (0.3)	1,516 (2.3)	1,650 (1.5)	162 (0.3)	2,007 (3.2)	2,169 (2)
	1 month-1 year	1,776 (3.7)	10,665 (16.4)	12,441 (11.0)	1,714 (3.7)	9,288 (15)	11,002 (10.1)
	1-5 year	15,540 (32)	29,719 (45.8)	45,259 (39.9)	14,213 (30.4)	27,560 (44.4)	41,773 (38.3)
	5-10 year	13,504 (27.8)	16,846 (26.0)	30,350 (26.8)	13,137 (28.1)	16,475 (26.5)	29,612 (27.2)
	≥ 10 year	17,633 (36.3)	6,098 (9.4)	23,731 (20.9)	17,534 (37.4)	6,002 (9.7)	23,536 (21.6)
fabrication process	Total manufacturing workers	32,946 (67.8)	48,022 (74.0)	80,968 (71.4)	32,037 (68.4)	46,042 (74.1)	78,079 (71.7)
	Operator	1,784 (3.7)	44,137 (68.1)	45,921 (40.5)	1,758 (3.8)	42,261 (68)	44,019 (40.4)
	Service engineer	14,954 (30.8)	2,541 (3.9)	17,495 (15.4)	14,513 (31)	2,522 (4.1)	17,035 (15.6)
	Process engineer	11,728 (24.1)	1,754 (2.7)	13,482 (11.9)	11,384 (24.3)	1,682 (2.7)	13,066 (12)
	Supervisor	3,324 (6.8)	2,186 (3.4)	5,510 (4.9)	3,303 (7.1)	2,168 (3.5)	5,471 (5)
	Utility	4,090 (8.4)	1,315 (2.0)	5,405 (4.8)	3,916 (8.4)	1,276 (2.1)	5,192 (4.8)
Assembly	Total manufacturing workers	6,465 (13.3)	19,767 (30.5)	26,232 (23.1)	6,184 (13.2)	19,024 (30.6)	25,208 (23.1)
	Operator	661 (1.4)	19,038 (29.4)	19,699 (17.4)	612 (1.3)	18,304 (29.5)	18,916 (17.4)
	Service engineer	4,118 (8.5)	1,523 (2.3)	5,641 (5.0)	3,937 (8.4)	1,512 (2.4)	5,449 (5)
	Process engineer	1,611 (3.3)	146 (0.2)	1,757 (1.5)	1,565 (3.3)	142 (0.2)	1,707 (1.6)
	Supervisor	884 (1.8)	830 (1.3)	1,714 (1.5)	871 (1.9)	824 (1.3)	1,695 (1.6)
	Utility	436 (0.9)	406 (0.6)	842 (0.7)	434 (0.9)	400 (0.6)	834 (0.8)
Person-years		389,105	443,406	832,512	340,220	378,630	718,850
Cases		153	114	267	201	145	346†

*The total might be less or more than the sum of the number of employees at each stratum because there were workers who were classified into more than one stratum or classified as unknown.
†Six persons of the cases in incidence analysis had double primary cancers.

Study subjects

Eligible workers were 113,443 for mortality and 108,933 for incidence (Table 1). The proportion of females was 57% of both cohorts. Age and occupation were differentiated by sex. The most common age group was 30-39 years old for males and 20-29 years old for females as of 2009. Among male workers, 75% were manufacturing workers, and among female workers, 94% were in the mortality cohort. For female works, 74% were involved in the fabrication process and 31% were involved in the assembly process, while the respective values for male workers were 68% and 13%, respectively.

When the mortality study ended in 2008, 0.2% of workers were deceased and the study subjects observed represented 832,512 person-years. The overall mean length of follow-up for mortality analysis was 7.3 years.

In the incidence study, 0.3% of cohorts were registered as having cancers until 2007, and the observed study subjects represented 718,849 person-years. The overall mean length of follow-up for incidence analysis was 6.6 years.

Data matching process

The cohort dataset was sent to the National Statistical Office (NSO) and the Korea Central Cancer Registry (KCCR) in order to match the deaths or cancers between the two datasets. The NSO has reported national statistics on the cause of death based on death certificates annually since 1992. The cancer registry has been operating nationwide since 1980 and covers more than 95% cases of cancer that occurred in Korea. It is assumed that all of the unmatched persons with these registries remained alive at the end of study. That is we consider there is no follow-up loss for these individuals. The NSO and KCCR provided OSHRI the information on matched cases of the cause of death or type of cancer by the closing date of the study according to the classification of the International Classification of Diseases (ICD)-10. The matched data were given to OSHRI after trimming the personal information to maintain confidentiality by deleting some digits of the resident registration number, or by changing the birth or hired date year. The identity of each case was protected because in most cases there were at least 2 workers with the same sex, age, employed year, and company. When trimming the date of hire, July 15th of each year of employment was used to calculate the person-years. This matching process with death or cancer incidence data was performed independently because both NSO and KCCR have their own data protection policy that they should not provide any information that makes it possible to identify patients. Consequently it was impossible to link the death and cancer incidence information of the subjects. Sixty-three workers who had been diagnosed with any kind of cancer before entering the cohort were excluded. Appropriate ethical approval was obtained, and the data for the study were treated in accordance with current legislation on personal information security.

Mortality and incidence ratios calculation

The cancer mortality and incidence ratios were calculated for all subjects and subgroups and they were classified by work duration, job categories, fabrication/assembly process, and the first year of employment. Standardized mortality ratios (SMRs) were calculated with the observed cases of deaths and divided by expected cases of deaths based on deaths in the Korean general population, which was standardized by sex, age (5-year age groups from 15 to 84), and calendar period (3 calendar periods of 1998-2001, 2002-2005, and 2006-2008).

The standardized incidence ratios (SIRs) of the cohort was calculated with the observed cases of cancers divided by the expected cases of cancers based on the cancer incidence of the Korean general population, which was standardized by sex, age (5-year age groups from 15 to 89), and calendar period (2 calendar periods of 1998-2002 and 2003-2007). Mortality and incidence rates of the reference population in the mid-year of each calendar period were used.

p-values and 95% confidence intervals (95% CIs) were calculated based on the assumption that deaths and cancers occurred with a Poisson distribution. Statistical analysis were done by PAMCOMP (Person-years and mortality computation program) [12] and LTAS (Life Table Analysis System) [13].

Results

Mortality analysis

The most common causes of death were injury, poisoning, and certain other consequences of external causes (S00-T98) (140 cases), followed by neoplasms (C00-D48) (75 cases) and disease of the circulatory system (I00-I99) (25 cases). The SMR for all cause mortality was 0.25 (95% CI 0.21-0.29) in males and 0.66 (95% CI 0.55-0.80) in females (Table 2). Mortality of most cancers was lower than expected. The SMR of leukemia was 0.39 (95% CI 0.08-1.14) in males with 2 deaths, and 1.37 (95% CI 0.55-2.81) in females with 7 deaths. The SMR of non-Hodgkin's lymphoma (NHL) increased to 1.33 (95% CI 0.43-3.09) in males with five cases and 2.5 (95% CI 0.68-6.40) in females with 4 cases, but they were not statistically significant.

Cancer incidence analysis

The SIR for all malignant neoplasm was 0.86 (95% CI 0.74-0.98) in males and 0.88 (95% CI 0.74-1.03) in females (Table

Table 2. Observed number of deaths of specific types of cancer, SMRs and 95% confidence interval

Disease group (ICD-10)	Male			Female		
	Obs	SMR	95% CI	Obs	SMR	95% CI
All cause	153	0.25	(0.21-0.29)	114	0.66	(0.55-0.80)
[C00-C97] Malignant neoplasm	48	0.44	(0.32-0.58)	24	0.79	(0.51-1.18)
[C00-C14] Lip, oral cavity and pharynx	2	1.05	(0.13-3.81)	0	0	(0.00-13.88)
[C15-C26] Digestive organs	25	0.36	(0.23-0.53)	9	0.91	(0.42-1.73)
(C16) Stomach	10	0.5	(0.24-0.91)	5	0.8	(0.26-1.86)
(C18) Colon	1	0.26	(0.01-1.44)	3	2.87	(0.59-8.39)
(C22) Liver and intrahepatic bile ducts	11	0.35	(0.17-0.62)	1	0.85	(0.02-4.71)
(C23-C24) Gallbladder & other and unspecified parts of biliary tract	1	0.44	(0.01-2.44)	0	0	(0.00-20.60)
(C25) Pancreas	2	0.53	(0.06-1.93)	0	0	(0.00-10.31)
[C30-C39] Respiratory and intrathoracic organs	3	0.23	(0.05-0.67)	1	0.54	(0.01-3.00)
(C33-C34) Trachea & Malignant neoplasm of bronchus and lung	3	0.25	(0.05-0.74)	1	0.63	(0.02-3.53)
[C40-C41] Bone and articular cartilage	1	1.08	(0.03-5.99)	0	0	(0.00-3.76)
[C43-C44] Skin	1	1.36	(0.03-7.59)	0	0	(0.00-8.35)
[C45-C49] Mesothelial and soft tissue	1	0.7	(0.02-3.90)	0	0	(0.00-3.96)
[C50-C50] Breast	1	8.56	(0.22-47.70)	2	0.84	(0.10-3.02)
[C51-C58] Female genital organs	-	-	-	0	0	(0.00-1.64)
[C60-C63] Male genital organs	0	0	(0.00-5.46)	-	-	-
[C64-C68] Urinary tract	1	0.55	(0.01-3.06)	0	0	(0.00-12.464)
[C70-C72] Brain and other parts of central nervous system	4	0.92	(0.25-2.35)	1	0.34	(0.01-1.87)
(C73) Thyroid gland	0	0	(0.00-14.21)	0	0	(0.00-64.24)
[C81-C96] Lymphoid, haematopoietic and related tissue	8	0.64	(0.28-1.26)	11	1.56	(0.78-2.78)
(C82-C85) Non-Hodgkin's lymphoma	5	1.33	(0.43-3.09)	4	2.5	(0.68-6.40)
(C91-C95) Leukaemia	3	0.39	(0.08-1.14)	7	1.37	(0.55-2.81)

Obs: observed, SMR: standardized mortality ratio, CI: confidence interval.

3). The SIR of NHL in females increased to 2.31 (95% CI 1.23-3.95), and it was statistically significant. The SIR of thyroid cancer in males increased to 2.11 (95% CI 1.49-2.89). The SIR of leukemia was 0.69 (95% CI 0.30-1.37) in males and 1.28 (95% CI 0.61-2.36) in females. Some groups of cancer also showed excessive incidence ratios, but they were not statistically significant, and they follow: lip, oral cavity, and pharynx for men (cases = 8, SIR 1.25, 95% CI 0.54-2.46), colon cancer for women (cases = 4, SIR 1.52, 95% CI 0.41-3.89), malignant melanoma for men (cases = 3, SIR 2.9, 95% CI 0.60-8.47), kidney cancer for men (cases = 13, SIR 1.82, 95% CI 0.97-3.12), corpus uteri cancer for women (cases = 4, SIR 1.53, 95% CI 0.42-3.92) and brain and central nervous system for men (cases = 9, SIR 1.37, 95% CI 0.62-2.59).

The SIR of leukemia in female workers slightly increased (cases = 10, SIR 1.28, 95% CI 0.61-2.36) (Table 4). The excess slightly decreased in female manufacturing workers (cases = 8, SIR 1.11, 95% CI 0.48-2.18). Among manufacturing workers, the excess slightly increased in assembly workers (cases = 4, SIR 1.69, 95% CI 0.46-4.32). The excess was greater in female workers employed before 1991 (cases = 2, SIR 5.92, 95% CI 0.72-21.37) than those employed after 1991 but not statistically significant. The number of cases in female workers employed before 1991 was only 2 and the confidence interval was very wide. In the current study, factory- or company-specific analyses were not possible due to the small number of cases. Among the 5 companies included, the number of cases ranged from 0 to 5 for males and 0 to 7 for females (not shown in tables).

Table 3. Observed number of cases of specific types of cancer, SIRs and 95% confidence interval

Disease group (ICD-10)	Male			Female		
	Obs	SIR	95% CI	Obs	SIR	95% CI
[C00-C97] Malignant neoplasm	201	0.86	(0.74-0.98)	145	0.88	(0.74-1.03)
[C00-C14] Lip, oral cavity and pharynx	8	1.25	(0.54-2.46)	1	0.31	(0.01-1.75)
[C15-C26] Digestive organs	88	0.68	(0.54-0.83)	19	0.87	(0.52-1.36)
(C15) Oesophagus	1	0.58	(0.01-3.26)	0	0	(0.00-55.12)
(C16) Stomach	44	0.84	(0.61-1.13)	12	0.93	(0.48-1.62)
(C18) Colon	9	0.63	(0.29-1.20)	4	1.52	(0.41-3.89)
(C19-C20) Rectosigmoid junction & rectum	12	0.83	(0.43-1.45)	1	0.48	(0.01-2.67)
(C22) Liver and intrahepatic bile ducts	18	0.46	(0.27-0.73)	1	0.39	(0.01-2.18)
(C23-C24) Gallbladder & other and unspecified parts of biliary tract	2	0.75	(0.09-2.71)	0	0	(0.00-8.54)
(C25) Pancreas	2	0.49	(0.06-1.77)	0	0	(0.00-5.31)
[C30-C39] Respiratory and intrathoracic organs	10	0.55	(0.26-1.01)	1	0.31	(0.01-1.73)
(C33-C34) Trachea & Malignant neoplasm of bronchus and lung	7	0.48	(0.19-0.98)	1	0.46	(0.01-2.54)
[C40-C41] Bone and articular cartilage	4	2	(0.54-5.12)	0	0	(0.00-1.83)
[C43-C44] Skin	6	1.56	(0.57-3.40)	0	0	(0.00-2.06)
(C43) Malignant melanoma of skin	3	2.9	(0.60-8.47)	0	0	(0.00-6.83)
[C45-C49] Mesothelial and soft tissue	1	0.31	(0.01-1.75)	1	0.4	(0.01-2.23)
[C50-C50] Breast	0	0	(0.00-16.71)	16	0.77	(0.44-1.26)
[C51-C58] Female genital organs	-	-	-	20	0.84	(0.51-1.29)
(C53) Cervix uteri	-	-	-	3	0.31	(0.06-0.91)
(C54) Corpus uteri	-	-	-	4	1.53	(0.42-3.92)
(C56) Ovary	-	-	-	9	0.92	(0.42-1.75)
[C60-C63] Male genital organs	1	0.19	(0.00-1.04)	-	-	-
[C64-C68] Urinary tract	17	1.36	(0.79-2.18)	0	0	(0.00-2.17)
(C64) Kidney, except renal pelvis	13	1.82	(0.97-3.12)	0	0	(0.00-3.04)
(C67) Bladder	5	1.06	(0.34-2.47)	0	0	(0.00-7.71)
[C70-C72] Brain and other parts of central nervous system	9	1.37	(0.62-2.59)	1	0.22	(0.01-1.22)
[C73-C75] Thyroid and other endocrine glands	41	2.19*	(1.57-2.97)	63	1	(0.77-1.28)
(C73) Thyroid gland	38	2.11*	(1.49-2.89)	62	0.99	(0.76-1.27)
[C81-C96] Lymphoid, haematopoietic and related tissue	19	0.78	(0.47-1.22)	23	1.54	(0.98-2.31)
(C81) Hodgkin's disease	1	0.9	(0.02-5.00)	0	0	(0.00-2.55)
(C82-C85) Non-Hodgkin's lymphoma	10	0.93	(0.45-1.71)	13	2.31*	(1.23-3.95)
(C91-C95) Leukaemia	8	0.69	(0.30-1.37)	10	1.28	(0.61-2.36)

Obs: observed, SIR: standardized incidence ratio, CI: confidence interval.
*Statistically significant at the 2-sided 5% level of significance.

The SIR of NHL significantly increased in females, especially in manufacturing workers (Table 5). Among manufacturing workers, the excess increased more in assembly operators (cases = 5, SIR 3.1, 95% CI 1.02-7.36). The excess was highest in female workers employed after 2004 (cases = 3, SIR 5.28, 95% CI 1.09-15.44) among the groups according to the first

Table 4. Leukemia (C91-C95) incidence : numbers and SIRs by selected subgroups

		Male			Female		
		Obs	SIR	95% CI	Obs	SIR	95% CI
Total*		8	0.69	(0.30-1.37)	10	1.28	(0.61-2.36)
Job	Office workers	2	0.63	(0.08-2.27)	2	3.49	(0.42-12.60)
	Manufacturing workers	6	0.72	(0.26-1.56)	8	1.11	(0.48-2.18)
Manufacturing worker	Assembly	0	0	(0.00-2.50)	4	1.69	(0.46-4.32)
	Fabrication	6	0.8	(0.29-1.75)	7	1.22	(0.49-2.52)
FAB manufacturing worker	Operator	1	2.06	(0.05-11.46)	6	1.15	(0.42-2.50)
	Service engineer	5	1.57	(0.51-3.66)	1	3.45	(0.09-19.23)
	Process engineer	1	0.34	(0.01-1.90)	0	0	(0.00-16.79)
	Supervisor	0	0	(0.00-3.59)	1	2.40	(0.06-13.38)
	Utility	1	1.16	(0.03-6.47)	1	6.44	(0.16-35.87)
Assembly manufacturing worker	Operator	0	0	(0.00-21.10)	4	1.78	(0.49-4.56)
	Service engineer	0	0	(0.00-4.26)	1	5.78	(0.15-32.20)
	Process engineer	0	0	(0.00-8.71)	0	0	(0.00-222.46)
	Supervisor	0	0	(0.00-13.60)	0	0	(0.00-22.77)
	Utility	0	0	(0.00-29.44)	1	22.14	(0.56-123.38)
Hire date	< 1991	5	1.43	(0.46-3.33)	2	5.92	(0.72-21.37)
	1992-1997	3	0.61	(0.12-1.77)	4	1.15	(0.31-2.95)
	1998-2003	0	0	(0.00-1.61)	3	0.98	(0.20-2.87)
	≥ 2004	0	0	(0.00-4.70)	1	1.06	(0.03-5.89)
Years worked	1 month-1 year	0	0	(0.00-11.07)	1	1.13	(0.03-6.28)
	1-5 year	0	0	(0.00-1.98)	4	1.38	(0.37-3.52)
	5-10 year	3	0.94	(0.19-2.74)	2	0.79	(0.10-2.86)
	≥ 10 year	5	0.82	(0.27-1.92)	3	2.46	(0.51-7.20)

Obs: observed, SIR: standardized incidence ratio, CI: confidence interval, FAB: fabrication.
*The total might be less or more than the sum of the number of cases at each stratum because there were workers who were classified into more than one stratum or classified as unknown.

year employed. Also, the excess was greater in female workers who worked for 1-5 years (cases = 6, SIR 2.94, 95% CI 1.08-6.39) than those who worked for 5-10 years and more than 10 years.

The excess of male thyroid cancer was observed (cases = 38, SIR 2.11, 95% CI 1.49-2.89), and this data was also investigated for male office workers (cases = 15, SIR 2.75, 95% CI 1.54-4.54). Among manufacturing workers, the excess was significant for process engineers (cases = 12, SIR 2.50, 95% CI 1.29-4.38). The excess was greatest for men first employed in 1992-1997 (cases = 20, SIR 2.78, 95% CI 1.70-4.30) among the groups according to the first year employed. The excess was significant for men who worked for more than 10 years (cases = 23, SIR 2.30, 95% CI 1.46-3.46).

The SIR of kidney cancer increased in males (cases = 13, SIR 1.82, 95% CI 0.97-3.12) and the SIR was marginally significant. But there were no cases of kidney cancer in females.

Discussion

The semiconductor industry is chemical-intensive, especially for the wafer fabrication process. Once it was thought to be a "clean" industry because of the clean-room, but there was concern of continuous multiple chemical exposures to workers from recirculated air for particle control [3]. Actually, there were some suspicious disease clusters mainly focused in can-

Table 5. Non-Hodgkin's lymphoma (C81-C85) incidence : numbers and SIRs by selected subgroups

		Male			Female		
		Obs	SIR	95% CI	Obs	SIR	95% CI
Total[†]		10	0.93	(0.45-1.71)	13	2.31*	(1.23-3.95)
Job	Office workers	2	0.60	(0.07-2.16)	0	0	(0.00-7.64)
	Manufacturing workers	8	1.08	(0.47-2.12)	13	2.53*	(1.34-4.32)
Manufacturing worker	Assembly	0	0	(0.00-2.77)	5	2.97	(0.96-6.92)
	Fabrication	8	1.21	(0.52-2.38)	8	1.96	(0.85-3.86)
FAB manufacturing worker	Operator	1	2.15	(0.05-11.98)	7	1.91	(0.77-3.94)
	Service engineer	3	1.13	(0.23-3.32)	0	0	(0.00-17.65)
	Process engineer	2	0.74	(0.09-2.67)	0	0	(0.00-21.26)
	Supervisor	2	1.90	(0.23-6.86)	0	0	(0.00-11.38)
	Utility	2	2.67	(0.32-9.64)	0	0	(0.00-31.72)
Assembly manufacturing worker	Operator	0	0	(0.00-20.57)	5	3.15*	(1.02-7.36)
	Service engineer	0	0	(0.00-5.12)	0	0	(0.00-31.27)
	Process engineer	0	0	(0.00-9.07)	0	0	(0.00-288.05)
	Supervisor	0	0	(0.00-13.26)	0	0	(0.00-29.95)
	Utility	0	0	(0.00-30.49)	0	0	(0.00-103.19)
Hire date	< 1991	3	0.76	(0.16-2.21)	1	3.19	(0.08-17.79)
	1992-1997	4	0.92	(0.25-2.37)	6	2.26	(0.83-4.92)
	1998-2003	1	0.53	(0.01-2.95)	3	1.44	(0.30-4.20)
	≥ 2004	2	3.45	(0.42-12.46)	3	5.28*	(1.09-15.44)
Years worked	1 month-1 year	0	0	(0.00-12.47)	0	0	(0.00-6.34)
	1-5 year	4	2.50	(0.68-6.41)	6	2.94*	(1.08-6.39)
	5-10 year	2	0.71	(0.09-2.57)	5	2.69	(0.87-6.28)
	≥ 10 year	4	0.66	(0.18-1.70)	1	1.03	(0.03-5.75)

Obs: observed, SIR: standardized incidence ratio, CI: confidence interval, FAB: fabrication.
*Statistically significant at the 2-sided 5% level of significance.
[†]The total might be less or more than the sum of the number of cases at each stratum because there were workers who were classified into more than one stratum or classified as unknown.

cers, reproductive disorders, and rare diseases in a few countries since the semiconductor industry began. For this reason, some studies were performed to investigate cancer risk [5-8], but a definitive association between work in semiconductor manufacturing and cancers was not found. This study was performed in response to leukemia concerns in the Korean semiconductor industry [1], and there is still a need for a broad epidemiological investigation on cancer risk of semiconductor workers throughout the world.

Overall mortality experience

The overall pattern of mortality and cancer incidence showed a substantial decrease in deaths from all causes (SMR 0.25, CI 0.21-0.29) and all cancers (SMR 0.44, CI 0.32-0.58) among men, and a less substantial decrease among women for all causes (SMR 0.66, CI 0.55-0.80) and all cancers (SMR 0.79, CI 0.51-1.18). The cancer incidence (all malignant neoplasm) was slightly lower than expected in both men (SIR 0.86, CI 0.74-0.98) and women (SIR 0.88, CI 0.74-1.03). From these results, an apparent healthy worker effect was inferred for both males and females, and it was stronger for males. Substantial members of the cohort were quite young and active workers, so a considerable healthy worker effect was not surprising. In addition, these semiconductor workers were expected to belong

Table 6. Thyroid cancer (C73) incidence : numbers and SIRs by selected subgroup

		Male			Female		
		Obs	SIR	95% CI	Obs	SIR	95% CI
Total†		38	2.11*	(1.49-2.89)	62	0.99	(0.76-1.27)
Job	Office workers	15	2.75*	(1.54-4.54)	10	1.67	(0.80-3.08)
	Manufacturing workers	23	1.83*	(1.16-2.74)	52	0.92	(0.69-1.21)
Manufacturing worker	Assembly	4	1.82	(0.50-4.66)	17	0.91	(0.53-1.46)
	Fabrication	20	1.77*	(1.08-2.74)	37	0.83	(0.58-1.14)
FAB manufacturing worker	Operator	0	0	(0.00-5.21)	29	0.74	(0.50-1.07)
	Service engineer	8	1.81	(0.78-3.56)	1	0.42	(0.01-2.31)
	Process engineer	12	2.50*	(1.29-4.38)	5	2.20	(0.71-5.13)
	Supervisor	3	1.74	(0.36-5.09)	7	1.68	(0.67-3.45)
	Utility	1	0.84	(0.02-4.70)	1	0.80	(0.02-4.44)
Assembly manufacturing worker	Operator	2	7.07	(0.86-25.54)	16	0.93	(0.53-1.51)
	Service engineer	3	2.53	(0.52-7.40)	0	0	(0.00-2.92)
	Process engineer	1	1.40	(0.04-7.79)	0	0	(0.00-22.86)
	Supervisor	0	0	(0.00-7.86)	0	0	(0.00-2.24)
	Utility	0	0	(0.00-20.34)	0	0	(0.00-10.22)
Hire date	< 1991	12	1.85	(0.95-3.23)	5	1.11	(0.36-2.60)
	1992-1997	20	2.78*	(1.70-4.30)	41	1.23	(0.88-1.67)
	1998-2003	6	1.84	(0.68-4.01)	13	0.66	(0.35-1.13)
	≥ 2004	0	0	(0.00-3.32)	3	0.61	(0.13-1.78)
Years worked	1 month-1 year	2	4.00	(0.48-14.45)	4	0.76	(0.21-1.94)
	1-5 year	4	1.46	(0.40-3.73)	16	0.74	(0.42-1.20)
	5-10 year	9	1.89	(0.86-3.58)	21	0.96	(0.59-1.47)
	≥ 10 year	23	2.30*	(1.46-3.46)	20	1.67*	(1.02-2.59)

Obs: observed, SIR: standardized incidence ratio, CI: confidence interval, FAB: fabrication.
*Statistically significant at the 2-sided 5% level of significance.
†The total might be less or more than the sum of the number of cases at each stratum because there were workers who were classified into more than one stratum or classified as unknown.

to the high socioeconomic status (SES) group because they are all regular workers of large enterprises. The overall low mortality of semiconductor workers in this study is compatible to previous studies on semiconductor workers in the US (SMR 0.68, 95% CI 0.66-0.71) [6], UK (SMR 0.45 for male, 0.73 for female) [5,14], and in Taiwan (SMR 0.27, 95% CI 0.22-0.33) [15].

Entering a company at an early age and the shorter working period of female workers might be one of the explanations for the mortality difference between male and female workers. Another possible explanation of the gender difference of mortality might result from stronger healthy worker effect for males than females. This is because the female general population is healthier than the male general population, for example, females drink and smoke less and the average life span of a female Korean is 7 year longer than that of a male. Mortality was lower in males than in female workers, a difference also seen in the UK [5] and Taiwan studies [15]. The majority (64%) of female workers had worked less than 5 years, whereas only 36% of male workers worked the same amount of time. The most common age group for males was 30-39 and 20-29 for females at the end of the study.

In our study, the cancer incidence difference between males and females was not shown, and this finding was also compatible to the UK study. It is possible that the healthy worker effect that was related to mortality was more profound in male workers than in female semiconductor workers. However, we are unable to explain why there was no difference in the overall incidence ratios.

Leukemia

Leukemia was the main cancer of public concern. Leukemia incidence was lower than expected (cases = 8, SIR 0.69, 95% CI 0.30-1.37) in males but not significant, and higher than expected (cases = 10, SIR 1.28, 95% CI 0.61-2.36) in females but also not significant. In the subgroup mortality analysis, the cases in each group were too small to detect any findings.

The risk of leukemia in the previous studies did not show consistent results. A cohort study in the UK Midland region [16] reported elevated incidence in males (cases = 1, SIR 1.59) and a lower than expected level in females (cases = 2, SIR 0.80, 95% CI 0.10-2.91), but the number of observations were too small. The UK National Semiconductor investigation [14] by the Health and Safety Executive (HSE) could not calculate the SMR and SIR because there was only one case of leukemia. A study at the US firm IBM reported that leukemia mortality was lower than expected (SMR 0.91, 95% CI 0.70-1.18) for workers in 2 semiconductor companies [6]. Another study at the same firm [8] showed a slightly high proportional cancer mortality ratio (PCMR) for leukemia for males (1.13, 95% CI 1.02-1.26) and for females (1.13, 95% CI 0.90-1.44). A US study that included multiple semiconductor facilities showed slightly lower leukemia mortality than expected (SMR 0.77, 95% CI 0.54-1.07) [17]. In a Taiwan study [15], significantly elevated mortality (SMR 3.33, 95% CI 1.08-7.77) was shown in male workers with a 5-year lag period.

The results of the present study and previous studies did not show strong evidence of a risk for leukemia. Leukemia is a very rare cancer, so a large cohort size and sufficient follow-up time are needed to observe meaningful findings. However, the majority of semiconductor studies, including this study, are limited by a small number of cases, so results are inconclusive.

Female NHL

Mortality for NHL was higher than expected in males (deaths = 5, SMR 1.33, 95% CI 0.43-3.09) and females (deaths = 4, SMR 2.50, 95% CI 0.68-6.40), but not statistically significant. The incidence of NHL was significantly higher than expected in females (cases = 13, SIR 2.31, 95% CI 1.23-3.95) but was in line with expectations in males (cases = 10, SIR 0.93, 95% CI 0.45-1.71). In the subgroup analysis of females, the SIR for manufacturing workers was higher than that of office workers, and the SIR for assembly workers was higher than that of fabrication workers among manufacturing workers. Incidences in groups with short work durations and those most recently employed were significantly higher than expected. This pattern reversal of the relationship between exposure duration and cancer incidence did not support the presence of an occupational carcinogen. The semiconductor industry has developed very rapidly, and concerns about hazards or negative health effects were particularly focused on older technology. But the possibility of work relatedness of NHL in semiconductor workers could not be ignored because subgroup analysis had more uncertainty for low numbers of person-years, and employment duration or employment year could not substitute for exposure level completely. In females, the portion of employees who worked for long periods was very small. For instance, workers who had worked over 10 years were accounted for less than 10% of the female cohort. This might be an explanation for the unstable result for subgroup analysis based on work duration.

Previous studies on semiconductor workers have inconsistently reported positive findings for NHL. Study at the US IBM firm reported that mortality for NHL was at the expected level (SMR 1.02, 95% CI 0.80-1.27) for workers in 2 semiconductor companies [6]. Another study at the same firm [8] reported a high proportional mortality ratio (PMR) and PCMR for both men (PMR 1.50, 95% CI 1.37-1.66, PCMR 1.36, 95% CI 1.23-1.49) and women (PMR 1.39, 95% CI 1.11-1.76, PCMR 1.22, 95% CI 0.97-1.54), but these findings need careful consideration because PMR and PCMR studies are based on only deceased subjects. Mortality for smoking-related cancer was significantly low in the IBM cohort studies [6], so PMRs or PCMRs for cancers at other site might be affected. PMR and PCMR findings need to be interpreted cautiously because an observed significant excess proportion could be caused either by a true elevated risk in the disease or by another disease having a substantially reduced proportion. A US study that included multiple semiconductor companies showed a lower than expected level of NHL (SMR 0.69, 95% CI 0.48-0.97) [17].

The main occupational risk factors for NHL that were studied include exposure to pesticides, solvents (for example benzene, trichloroethylene [TCE]), and radiation. But the reports on the NHL risk of these occupational factors are not consistent and there is no definite occupational risk factor for NHL known so far [18,19]. For this reason and the lack of individual exposure data, in this cohort study we were not able to explore the causative agents in semiconductors in Korea. In order to clarify the work-related risk of NHL, detailed toxicological explanations and experimental and epidemiological studies would be required.

Risks for NHL and leukemia showed marked gender differences. There is a job discrepancy between males and females, in that the portion of manufacturing workers among females is much larger than that among males. In the case of leukemia, this difference comparatively decreased in the analysis that restricted to manufacturing workers, but the gender difference for NHL risk did not decrease in the subgroup analysis and it was more profound in assembly manufacturing workers. Generally, female workers are engaged in assembly line and male workers maintain equipment required for production. But compared to workers in fabrication process, those in the assembly process have lower potential exposures to chemicals and it is not thought that there were potential exposure differences between males and females.

Male thyroid cancer

There was no death that resulted from thyroid cancer, but male incidence was significantly higher than expected (cases = 38, SIR 2.11, 95% CI 1.49-2.89). In females, the incidence was as expected (cases = 62, SIR 0.99, 95% CI 0.76-1.27). In the subgroup analysis of male workers, incidences were higher than expected in office and manufacturing workers, employees hired before 1998, and those employed for more than 10 years. The SIR for office workers was higher than that of manufacturing workers. SIRs of groups divided by employed years tended to increase in groups with long periods of work. Because high incidence ratios were distributed over various subgroups, it was hard to select suspected at-risk work groups.

There are few studies available that present the thyroid cancer risk in semiconductor industry workers. A study at the US firm IBM [7] reported that the incidence for thyroid cancer was lower than or the same as expected (SMR 0.71, 95%CI 0.43-1.11) for workers in an IBM facility that made semiconductors. Another study at the US firm IBM [8] showed a high PCMR for both men (PCMR 1.91, 95% CI 1.43-2.56) and women (PCMR 1.51, 95% CI 0.82-2.78). A US study including multiple semiconductor companies showed expected levels of thyroid cancer (SMR 0.66, 95% CI 0.02-3.67) [17].

Thyroid cancer is a common endocrine tumor and a well known risk factor for thyroid cancer is ionizing radiation [20]. Semiconductor manufacturers have an 'Implant' process in which workers have the possibility of radiation exposure. In this cohort study, we could not separate workers in radiation-related process. But it is not presumed that thyroid cancer cases were clustered in specific process because there were many cases in the office worker group. As for the NHL finding, a detailed analysis regarding toxicological explanations and a nested case-control study will be needed.

Thyroid cancer is regarded as a disease easily affected by over diagnosis bias or detection bias in epidemiological research. Some researchers thought that the rapid increase of thyroid cancer incidence worldwide was associated with an increased detection rate [21]. The possibility of detection bias is supported by the fact that subjects were mostly from the high SES population. High incidence in male office workers and highly educated groups (data not shown) might be associated with this result. But there is no definitive evidence of detection bias.

Other specific cancer

Although it was not statistically significant, the SIR of kidney cancer increased in males (cases = 13, SIR 1.82, 95% CI 0.97-3.12) and this was marginally significant. But there were no cases of kidney cancer in females. Previous studies did not show consistent results for kidney cancer. The UK Midland region study [16] reported elevated incidence in females (cases = 4, SIR 1.31, 95% CI 0.36-3.36) and there was no case observed in males. A study at the US firm IBM reported that kidney cancer mortality was at the expected level (SMR 0.95, 95% CI 0.69-1.29) for workers in the 2 semiconductor companies [6]. Another study at the same firm [8] showed a slightly high proportional cancer mortality ratio (PCMR) for kidney cancer for both men (PCMR = 1.36, 95% CI 1.21-1.53) and women (PCMR = 1.20, 95% CI 0.85-1.70). A US study that included multiple semiconductor facilities showed slightly lower kidney cancer mortality than expected (SMR 0.74, 95% CI 0.46-1.14) [17]. The UK National Semiconductor investigation [14] by the HSE analyzed the combined risk of genitourinary cancer and the incidence was lower than expected in both males (cases = 11, SIR = 0.82, 95% CI 0.41-1.47) and females (cases = 11, SIR = 0.67, 95% CI 0.33-1.20).

The incidence of malignant melanoma was considerably higher than expected in males (SIR = 2.9, 95% CI 0.60-8.47), although the confidence interval was very wide. This result was based on only 3 cases and there were no cases observed in females. Though the evidence is inconclusive, these results with large effect estimates should be noticed and be followed-up.

Strengths and weaknesses

This study is an investigation of the semiconductor industry in Korea, which means that it covers all major companies with a wafer fabrication process; therefore, selection bias due to geographic restriction was limited. Studies conducted in the UK National Semiconductor could not extend to the entire industry in the UK because pre-existing evidence was not enough to justify the commitment of resources [5]. Studies in the US firm IBM were also limited to eligible companies [6,7,17], and results may have been geographically biased. Our study was conducted by OSHRI of KOSHA, on behalf of the Ministry of Employment and Labor in Korea under the Occupational Safety and Health Act.

An additional strength of this study is the large number of study subjects in the fabrication process. The numbers of workers for mortality and incidence analyses in our study were 113,443 and 108,933, respectively, and person-years of mortality and incidence were 832,512 and 718,849, respectively. In the UK, the HSE study was conducted on 4,388 workers and 55,014 person-years in 2003 and it was updated in 2010 to 84,733 person-years [14]. Studies on the East Fishkill and Burlington factories in the US had larger numbers of workers (45,492 and 29,962, respectively) and person-years (813,961 and 464,390, respectively). In the Taiwan study, the number of workers was 47,426 [15]. Therefore, our cohort included relatively large numbers of workers compared with other studies. We also tried to assess non-fatal and fatal cancers for SMR and SIR calculations. The most recently reported study on the semiconductor industry in the US was conducted on 100,081 workers with 1,490,486 person-years [17]. However, only 37,225 workers that were involved in the fabrication process were assessed.

There were also limitations in our study. The cohort was built in 1998, but almost all the factories were established before 1998, so many earlier workers were excluded from the cohort. In the case that there were cancer deaths or occurrences in the workers retired before 1998, there could be an underestimate of the cancer risk because of the healthy worker survival effect. To consider this limitation, the year of 1998 was used to classify employees in subgroup analysis with respect to the hired dates of workers. It is assumed that all of the unmatched workers with the death or cancer registry remained alive at the end of the study. These registries covers nearly the entire nation, but if some of the workers had emigrated from Korea to another country after retirement and there were deaths or cancer occurrences among them during the study period, then the mortality rate or incidence rate of this cohort would be artificially lowered. But the emigration rate of Korean people has been very low (lower than 0.04% per year from 2002 to 2008) [22], so it is expected that underestimation of the risk due to this aspect is not strong. The observed period (6.6 years for incidence and 7.5 years for mortality) was not long enough to obtain stable results of cancer risk. In the UK National Semiconductor study, the mean length of follow-up was 12.5 years [5], and the US IBM factories were studied for more than 30 years [6]. In the present study, the majority of the subjects were young at the end of follow-up and cases were sparse for subgroups because of the long latency of cancer development.

There might be a possibility of misclassification for job groups because subjects were categorized by researchers and company staff based on the name of the department and job on the employment records. Information relating to non-occupational risk factors, like family history, was not considered and occupational exposure to specific agents on the personal level were not available. Information on the list of chemicals and exposure levels were reported in other studies [23]. We did not attempt to analyze data using internal comparison because of the small size of the office worker group; therefore, there might be a potential distortion due to the healthy worker effect and selection bias, like the detection bias from the relatively high SES.

In conclusion, there was no significant increase of leukemia in the semiconductor industry in Korea. However, NHL in females and thyroid cancer in males were significantly increased even though there was no definitive association between work and those diseases in subgroup analysis by work duration. This result should be interpreted cautiously and longer follow-up study is needed, because the majority of the cohort was young and the number of cases was very small. Also, a nested case-control study for female NHL and male thyroid cancer is needed to clarify the work-related risk of the cancers.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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