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Study Profile

Rationale, design, and profile of the Three-Prefecture Cohort in Japan: A 15-year follow-up

Junya Sado [a], Tetsuhisa Kitamura [a], Yuri Kitamura [a,*], Ling Zha [a], Rong Liu [a], Tomotaka Sobue [a], Yoshikazu Nishino [b], Hideo Tanaka [c], Tomio Nakayama [d], Ichiro Tsuji [e], Hidemi Ito [c], Takaichiro Suzuki [d], Kota Katanoda [f], Suketami Tominaga [c], for the Three-Prefecture Cohort Study Group

[a] Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
[b] Department of Epidemiology and Public Health, Kanazawa Medical University, Kahoku, Ishikawa, Japan
[c] Aichi Cancer Center, Nagoya, Japan
[d] Center of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[e] Division of Epidemiology, Devepartment of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[f] Division of Surveillance, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

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ABSTRACT

Background: We reutilized the existing Three-Prefecture Cohort to evaluate the relationship between lifestyle factors and the incidence or mortality from non-communicable diseases.
Methods: This study was a prospective population-based observation conducted from the 1980s to 2000 in three prefectures (Miyagi, Aichi, and Osaka) in Japan. The study subjects were residents aged ≥40 years who received a questionnaire. The follow-up period was 15 years from the baseline survey in each study area. A self-administered questionnaire, which included items on participants' demographic factors and lifestyle characteristics, was administered. Vital status and date of death were collected from residence certificates by the local government, and cause of death was identified using vital statistics. Cancer incidence and the date of diagnosis were collected from local cancer registry data.
Results: A total of 46,421 men and 54,189 women were eligible for our analysis. The person-years of follow-up for cancer incidence were 464,664 and 567,271 for men and women, respectively, and those for death were 527,940 and 648,601 for men and women, respectively. There were 8479 cancer incidences (5106 men and 3373 women) and 20,240 total deaths (11,156 men and 9084 women). The stomach was the most common cancer incidence site for both men (25.6%) and women (18.6%). The leading cause of death was cancer among men (35.0%) and cardiovascular disease among women (41.0%).
Conclusions: The Three-Prefecture Cohort Study enabled us to reveal the association of multiphasic lifestyle factors with cancer incidence and mortality. The study will also allow us to conduct a pooled analysis in combination with other large-scale cohorts.

Introduction

A cohort study is one of the ways to evaluate the relationship between lifestyle factors and the incidence or mortality from non-communicable diseases. Although huge amounts of money and long-term observation are needed to conduct a cohort study, such a design could minimize selection bias and maximized external validity. Large-scale prospective cohorts focused on healthy populations (e.g., the Japan Collaborative Cohort [JACC] Study[1] or the Japan Public Health-Based Prospective Cohort [JPHC] Study[2]) have been conducted since 1980s in Japan. There have also been large cohort studies worldwide, such as the National Institutes of Health–American Association of Retired Persons Diet and Health

* Corresponding author. Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamada-Oka, Suita, Osaka 565-0871, Japan.
E-mail address: ytkitamura@envi.med.osaka-u.ac.jp (Y. Kitamura).
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Table 1
Participants of the Three-Prefecture Cohort study.

	Miyagi Prefecture		Aichi Prefecture		Osaka Prefecture		Total
	Sendai-City (6 areas in Aoba and Miyagino wards)	Wakuya/Tajiri-Towns (Entire towns)	Nagoya-City (5 areas in Chigusa ward)	Inuyama-City (2 areas in the city)	Osaka-City (Higashinari ward)	Nose/Kanan/Kumatori-Town (Entire towns)	
All residents aged ≥40 years old	25,237	15,891	24,489	12,854	39,307	21,230	139,008
Delivered questionnaires	17,805	14,926	23,331	12,815	27,051	21,101	117,029
Responded questionnaires	17,195	14,574	21,535	12,003	20,665	18,565	104,537
Response rate (%)[a]	(68.1)	(91.7)	(87.9)	(93.4)	(52.6)	(87.4)	(75.2)
Response rate (%)[b]	(96.6)	(97.6)	(92.3)	(93.7)	(76.4)	(88.0)	(89.3)

[a] Denominator was subjects who were all residents aged ≥40 years old.
[b] Denominator was subjects who were delivered the self-administrated questionnaire.

Study in the United States,[3] the European Prospective Investigation into Cancer and Nutrition in Europe,[4] and the Korean Multi-center Cancer Cohort Study in Korea.[5] Indeed, many findings have been obtained from these studies.

The Three-Prefecture Cohort Study was a prospective population-based observational study launched in 1983, which targeted approximately 100,000 inhabitants in Miyagi Prefecture, Aichi Prefecture, and Osaka Prefecture in Japan and conducted a questionnaire survey to reveal the association of multiphasic life-style factors with cancer incidence or mortality. Here, we briefly described the study concept and the cohort population's profile.

Materials and methods

Study design and settings

This cohort, which has been under prospective observation since 1983, was studied to assess the long-term effects of air pollution on mortality from lung cancer and respiratory diseases.[6,7] The study areas were chosen because they contained a national air monitoring station and had well-managed cancer surveillance systems in 1983, including eight selected urban/rural areas in Miyagi Prefecture (Sendai City and Wakuya/Tajiri Town), Aichi Prefecture (Nagoya City and Inuyama City), and Osaka Prefecture (Osaka City and Nose/Kanan/Kumatori Town). Since the 1970s, there has been a network of ambient air monitoring stations in Japan operated by the Ministry of Environment (formerly the National Environment Agency) and local governments. In this study, we defined rural areas as cities/towns with general air pollution monitoring stations (control area) and urban areas as cities/towns with automobile exhaust gas measurement stations (pollution area).[6] Self-administered questionnaires in sealed envelopes were distributed by hand to targeted individuals in cooperation with the municipal government in each area and were collected after a set period of time. The study committee, consisting of health center directors, local officials, and residents' association representatives, was established to protect personal information of the participants and ensure the accuracy of the study. In this study, we merged individuals' data with their cancer incidence information based on personal name, gender, and date of birth. The proportion of death certificate only (DCO) deaths in each area was 9.1%–17.8% in Miyagi Prefecture,[8] 28.1%–32.6% in Aichi Prefecture,[9] and 20.7%–23.4% in Osaka Prefecture.[10]

The study subjects were residents aged ≥40 years who received a questionnaire, and they were enrolled between 1983 and 1985. The investigation was begun in Osaka Prefecture in 1983, in Miyagi

Table 2
Distribution of cohort participants at baseline by gender, age, and region.

	Age at baseline, years										Total	%
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85		
Men												
Japan census population 1985 (x1,000)	4494	4053	3898	3391	2349	1771	1486	997	546	247	23,232	
%	19.3	17.4	16.8	14.6	10.1	7.6	6.4	4.3	2.4	1.1		100.0
Three-prefecture cohort participants	8082	7735	7795	6804	5018	4067	3410	2153	973	384	46,421	
%	17.4	16.7	16.8	14.7	10.8	8.8	7.3	4.6	2.1	0.8		100.0
Miyagi Prefecture (urban)	1137	1161	1194	1057	859	765	586	371	189	72	7391	15.9
Miyagi Prefecture (rural)	903	1020	1213	1082	784	607	490	333	116	53	6601	14.2
Aichi Prefecture (urban)	1841	1821	1760	1358	1035	818	675	442	220	74	10,044	21.6
Aichi Prefecture (rural)	1095	989	963	823	561	476	377	250	109	49	5692	12.3
Osaka Prefecture (urban)	990	1161	1265	1183	927	764	718	440	193	67	7708	16.6
Osaka Prefecture (rural)	2116	1583	1400	1301	852	637	564	317	146	69	8985	19.4
Women												
Japan census population 1985 (x1,000)	4554	4140	3971	3574	3011	2394	2046	1438	906	525	26,559	
%	17.1	15.6	15.0	13.5	11.3	9.0	7.7	5.4	3.4	2.0		100.0
Three-prefecture cohort participants	8522	8522	8337	7814	6604	5196	4261	2722	1471	740	54,189	
%	15.7	15.7	15.4	14.4	12.2	9.6	7.9	5.0	2.7	1.4		100.0
Miyagi Prefecture (urban)	1318	1447	1508	1379	1234	937	740	453	257	110	9383	17.3
Miyagi Prefecture (rural)	938	1161	1354	1268	1009	758	717	391	220	154	7970	14.7
Aichi Prefecture (urban)	1911	1944	1785	1621	1361	1020	843	578	264	141	11,468	21.2
Aichi Prefecture (rural)	1071	1050	897	869	711	638	459	346	171	94	6306	11.6
Osaka Prefecture (urban)	1264	1380	1404	1377	1246	1031	820	501	291	125	9439	17.4
Osaka Prefecture (rural)	2020	1540	1389	1300	1043	812	682	453	268	116	9623	17.8

Table 3
Selected baseline demographic and lifestyle characteristics of participants by gender.

	Men	Women
	(n = 46,421)	(n = 54,189)
Mean age, years (standard deviation)	56.1 (11.2)	57.1 (11.6)
Regions, n (%)		
Miyagi, urban	7391 (15.9)	9383 (17.3)
Miyagi, rural	6601 (14.2)	7970 (14.7)
Aichi, urban	10,044 (21.6)	11,468 (21.2)
Aichi, rural	5692 (12.3)	6306 (11.6)
Osaka, urban	7708 (16.6)	9439 (17.4)
Osaka, rural	8985 (19.4)	9623 (17.8)
Health insurance type, n (%)		
National health insurance	20,877 (45.0)	25,263 (46.6)
Government/union-managed health insurance	19,267 (41.5)	20,864 (38.5)
Mutual aid associations health insurance	3897 (8.4)	4250 (7.8)
Others	577 (1.2)	891 (1.6)
Missing	1803 (3.9)	2921 (5.4)
History of hypertension, n (%)		
Current	8289 (17.9)	10,138 (18.7)
Past	1709 (3.7)	2189 (4.0)
Never	19,820 (42.7)	23,811 (43.9)
Missing	16,603 (35.8)	18,051 (33.3)
History of diabetes, n (%)		
Current	2725 (5.9)	1803 (3.3)
Past	738 (1.6)	275 (0.5)
Never	20,895 (45.0)	25,586 (47.2)
Missing	22,063 (47.5)	26,525 (48.9)
Body mass index, n (%)		
≤19.0 kg/m2	4310 (9.3)	6255 (11.5)
19.0–21.9 kg/m2	14,995 (32.3)	17,153 (31.7)
22.0–24.9 kg/m2	17,155 (37.0)	17,294 (31.9)
25.0–29.9 kg/m2	7528 (16.2)	9378 (17.3)
≥30.0 kg/m2	515 (1.1)	1130 (2.1)
Missing	1918 (4.1)	2979 (5.5)
Alcohol drinking, n (%)		
Never	7122 (15.3)	26,119 (48.2)
Former	2787 (6.0)	1094 (2.0)
Current occasional	11,884 (25.6)	13,497 (24.9)
Current almost daily	21,776 (46.9)	2942 (5.4)
Missing	2852 (6.1)	10,537 (19.4)
Smoking status, n (%)		
Never	7411 (16.0)	37,281 (68.8)
Former	10,805 (23.3)	1746 (3.2)
Current	23,969 (51.6)	5199 (9.6)
Missing	4236 (9.1)	9963 (18.4)
Green and yellow vegetable consumption, n (%)		
≤1–2 times/month	3311 (7.1)	2183 (4.0)
1–2 times/week	10,320 (22.2)	8563 (15.8)
3–4 times/week	12,623 (27.2)	14,918 (27.5)
Almost daily	17,509 (37.7)	24,445 (45.1)
Missing	2658 (5.7)	4080 (7.5)
Non-green and non-yellow vegetable consumption, n (%)		
≤1–2 times/month	1491 (3.2)	1111 (2.1)
1–2 times/week	6634 (14.3)	5229 (9.6)
3–4 times/week	12,267 (26.4)	12,816 (23.7)
Almost daily	23,782 (51.2)	31,276 (57.7)
Missing	2247 (4.8)	3757 (6.9)
Fruit consumption, n (%)		
≤1–2 times/month	5040 (10.9)	2452 (4.5)
1–2 times/week	9631 (20.7)	6291 (11.6)
3–4 times/week	10,303 (22.2)	10,649 (19.7)
Almost daily	18,308 (39.4)	30,535 (56.3)
Missing	3139 (6.8)	4262 (7.9)
Miso soup consumption, n (%)		
≤1–2 times/month	3141 (6.8)	3823 (7.1)
1–2 times/week	7127 (15.4)	8473 (15.6)
3–4 times/week	8035 (17.3)	9746 (18.0)
Almost daily	25,913 (55.8)	28,213 (52.1)
Missing	2205 (4.8)	3934 (7.3)
Pickled vegetable consumption, n (%)		
Scarcely any	2296 (4.9)	2095 (3.9)
1–2 times/month	2311 (5.0)	2380 (4.4)
1–2 times/week	5114 (11.0)	5340 (9.9)
3–4 times/week	6508 (14.0)	6753 (12.5)
Almost daily	27,016 (58.2)	32,802 (60.5)
Missing	3176 (6.8)	4819 (8.9)
Type of job, n (%)		
Professional technical and civil workers	3835 (8.3)	2805 (5.2)
Managerial workers	959 (2.1)	98 (0.2)
Clerical workers	5415 (11.7)	5197 (9.6)
Sales workers	5495 (11.8)	3663 (6.8)
Agricultural, forestry and fisheries workers	2844 (6.1)	3127 (5.8)
Construction workers	92 (0.2)	9 (0.0)
Workers in transport and communications	1814 (3.9)	309 (0.6)
Craftsman, production process worker, and laborers	9537 (20.5)	4740 (8.7)
Workers in security	567 (1.2)	18 (0.0)
Service workers	1069 (2.3)	2750 (5.1)
Unemployed	1284 (2.8)	10,666 (19.7)
Missing	13,510 (29.1)	20,807 (38.4)

Prefecture in 1984, and in Aichi Prefecture in 1985. The number of questionnaire responders was 17,195/17,805 (96.6%) in Sendai City, 14,574/14,926 (97.6%) in Wakuya/Tajiri Town, 21,535/23,331 (92.3%) in Nagoya City, 12,003/12,815 (93.7%) in Inuyama City, 20,665/27,051 (76.4%) in Osaka City, and 18565/21,101 (88.0%) in Nose/Kanan/Kumatori Town (Table 1). Of 104,537 responders, a total of 100,629 were included as subjects, after excluding those who answered a questionnaire in duplicate or did not provide their name/gender/date of birth because investigators could not follow up the outcome data in the Three-Prefecture Cohort study.

Questionnaire

Baseline questionnaire items included the following: area of residence, gender, height, weight, health condition at that time, past medical history, type of insurance, health check-up/cancer screening history, frequency of food intake, smoking, alcohol drinking status, parent's medical history, smoking status of co-habitants, house environment, occupation (such as the longest period of employment), and reproductive history (only for women). Medical history included: past history of diabetes mellitus, hypertension, stroke, and emphysema; and stomach cancer screening by x-ray examination, blood pressure measurement, and uterus cancer screening (only for women). Food intake frequency of items, such as rice, bread, meat, fish, eggs, milk, green/yellow vegetables, non-green/yellow vegetables, fruit, miso soup, and pickled vegetables, as well as drinking beverages, such as green tea, black tea, and coffee, was assessed categorically.

Follow-up

The follow-up period was defined as 15 years from the baseline survey in each study area, except for cancer incidence data in Miyagi Prefecture, for which follow-up was 9 years. The cohorts were followed from 1984 to 1999 in Miyagi Prefecture, from 1985 to 2000 in Aichi Prefecture, and from 1983 to 2000 in Osaka Prefecture. Vital status, date of death, and date of move-out from the study area were confirmed by the local government using residence certificates. Cause of death was identified using death certificate. Cancer incidence and the date of diagnosis were collected from local cancer registry data.

Statistical analysis

The definition of disease was determined based on the International Classification of Diseases 9th version (ICD-9) for data

collected from 1983 to 1994 and or the 10th version (ICD-10) for data collected from 1995 to 2000 in this study. We counted the number of incident cancers and deaths of all cancer and cancer of individual sites, and also the number of deaths according to cause of death. When mortality rates were calculated, person-years of follow-up for mortality were counted from the date of the baseline survey to the date of death, date of move-out from the study area, or the end of 15-year follow-up (whichever occurred first). For cancer incidence rates, date of diagnosis of first primary cancer was added to the above list. In addition, standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) of all-cause and all cancer were calculated using age-adjusted mortality/incidence rate, which was calculated using 5-year age-specific rates in each year according to the cancer registry and vital statistics in Japan.[11,12] Statistical analyses were implemented using STATA version 13 MP (Stata Corp., College Station, TX, USA).

Ethics

The study was approved by the institutional review board of the National Cancer Center and the Ethics Committee of Osaka University School of Medicine. We received permission from the municipal governments to survey residents. The response to the questionnaire by participant was considered consent to participate in the survey. Tohoku University, Aichi Cancer Center, and Osaka Medical Center for Cancer and Cardiovascular Diseases were primarily responsible for analyzing information on baseline surveys, linking with cancer incidence and cause of death data, and altering the data set to unlinkable anonymized data. Although the National Cancer Center had originally managed the integrated datasets, Osaka University manages them at present. In the Three-Prefecture Cohort study, researchers only analyzed unlinkable anonymous data.

Results

Of 100,629 participants aged 40–99 years old at baseline, 19 (0.02%) were excluded because their responses preceded the date of beginning of follow-up, which was unified in each area after various dates of individual response to the questionnaire. As a result, 46,421 men and 54,189 women were eligible for this study. Details of the distribution of cohort participants at baseline by sex, age, and region are noted in Table 2. The person-years of follow-up for cancer incidence were 464,664 and 567,271 for men and women, respectively, and the person-years for death were 527,940 and 648,601 for men and women, respectively.

Table 3 shows selected baseline characteristics of participants by sex. Mean age among men and women was 56.1 and 57.1 years, respectively, and the proportion of participants with a body mass index of 22.0–24.9 kg/m^2 was 37.0% among men and 31.9% among women. The proportion of current drinkers of alcoholic beverages was 46.9% for men and 5.4% for women, and the proportion of current smokers was 51.6% for men and 9.6% for women. Regarding the longest period occupational classification, the proportion of participants engaged in clerical work was 11.7% among men and 9.6% among women, and the proportion of those unemployed was 2.8% among men and 19.7% among women.

Table 4 shows the follow-up results, Table 5 lists major types of incident cancers, and Table 6 lists major causes of death by gender. There were 20,240 total deaths (20.1%; 11,156 men and 9084 women), and 20,281 move-outs (20.2%; 9145 men and 11,136 women) (Table 4). The SIR of all cancers was 0.96 among men and

Table 4
15-year follow-up status until 2000 by gender and age.

	Age at baseline, years										Total
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85	
Men											
Number at baseline	8082	7735	7795	6804	5018	4067	3410	2153	973	384	46,421
Number of all cancer incidences	215	371	665	891	841	802	712	414	159	36	5106
% (Number of all cancer incidences/Number at baseline)	2.7	4.8	8.5	13.1	16.8	19.7	20.9	19.2	16.3	9.4	11.0
Number of deaths	320	506	960	1268	1407	1790	2054	1642	850	359	11,156
% (Number of all cause deaths/Number at baseline)	4.0	6.5	12.3	18.6	28.0	44.0	60.2	76.3	87.4	93.5	24.0
Number of all cancer deaths	135	230	463	642	615	641	626	375	140	35	3902
% (Number of all cancer deaths/Number at baseline)	1.7	3.0	5.9	9.4	12.3	15.8	18.4	17.4	14.4	9.1	8.4
Number who left study area	2359	1991	1608	1151	735	558	421	226	80	16	9145
% (Number who left study area/Number at baseline)	29.2	25.7	20.6	16.9	14.6	13.7	12.3	10.5	8.2	4.2	19.7
Person-years (incidence)	87,758	83,560	83,345	71,783	50,831	37,773	28,223	14,550	5175	1666	464,664
Incidence rate (all cancer per 1000 person-years)	2.4	4.4	8.0	12.4	16.5	21.2	25.2	28.5	30.7	21.6	11.0
Person-years (mortality)	96,389	93,649	95,428	83,102	59,579	44,107	32,193	16,278	5500	1714	527,940
Mortality rate (all cause per 1000 person-years)	3.3	5.4	10.1	15.3	23.6	40.6	63.8	100.9	154.5	209.4	21.1
Mortality rate (all cancer per 1000 person-years)	1.4	2.5	4.9	7.7	10.3	14.5	19.4	23.0	25.5	20.4	7.4
Women											
Number at baseline	8522	8522	8337	7814	6604	5196	4261	2722	1471	740	54,189
Number of cancer incidences	229	291	386	483	513	539	478	296	121	37	3373
% (Number of all cancer incidences/Number at baseline)	2.7	3.4	4.6	6.2	7.8	10.4	11.2	10.9	8.2	5.0	6.2
Number of deaths	181	301	446	662	946	1365	1712	1648	1157	666	9084
% (Number of all cause deaths/Number at baseline)	2.1	3.5	5.3	8.5	14.3	26.3	40.2	60.5	78.7	90.0	16.8
Number of all cancer deaths	98	170	211	286	325	410	404	278	115	34	2331
% (Number of all cancer deaths/Number at baseline)	1.1	2.0	2.5	3.7	4.9	7.9	9.5	10.2	7.8	4.6	4.3
Number who left study area	2242	2051	1693	1483	1233	1012	758	440	166	58	11,136
% (Number who left study area/Number at baseline)	26.3	24.1	20.3	19.0	18.7	19.5	17.8	16.2	11.3	7.8	20.6
Person-years (incidence)	94,984	94,636	92,190	85,763	71,427	53,084	40,224	22,468	9322	3172	567,271
Incidence rate (all cancer per 1000 person-years)	2.4	3.1	4.2	5.6	7.2	10.2	11.9	13.2	13.0	11.7	5.9
Person-years (mortality)	105,776	107,461	107,287	100,096	83,052	60,982	46,008	24,740	9927	3272	648,601
Mortality rate (all cause per 1000 person-years)	1.7	2.8	4.2	6.6	11.4	22.4	37.2	66.6	116.6	203.5	14.0
Mortality rate (all cancer per 1000 person-years)	0.9	1.6	2.0	2.9	3.9	6.7	8.8	11.2	11.6	10.4	3.6

Table 5
Distribution of number of cancer incidence by site, gender, and age at baseline during 15-year follow-up.

ICD10	ICD9		Age at baseline, years										Total	%
			40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85		
Men														
C00-C97	140–208.9	all cancer	215	371	665	891	841	802	712	414	159	36	5106	100.0
C15	150–150.9	Esophagus	14	20	25	43	35	29	29	8	4	0	207	4.1
C16	151–151.9	Stomach	52	94	180	235	224	191	187	95	34	10	1302	25.5
C18	153–153.9	Colon	26	40	78	74	75	75	52	37	19	1	477	9.3
C19-20	154–154.9	Rectum	18	28	29	44	46	33	23	21	3	1	246	4.8
C22	155–155.9	Liver and intrahepatic bile ducts	24	58	117	137	82	83	57	33	15	2	608	11.9
C23	156	Gall bladder	0	2	3	3	2	3	4	2	0	0	19	0.4
C24	156.1–156.9	Other and unspecified parts of biliary tract	4	4	11	9	11	20	15	8	4	2	88	1.7
C25	157–157.9	Pancreas	10	10	19	34	37	33	29	21	8	2	203	4.0
C33-34	162–162.9	Lung	24	38	79	120	160	174	160	85	25	8	873	17.1
C61	185–185.9	Prostate	1	7	10	39	31	41	35	25	15	2	206	4.0
C64	189–189.1	Kidney	3	10	8	21	14	11	8	7	0	0	82	1.6
C65-67	189.2–189.4	Urothelial tract	2	9	4	11	9	13	11	3	2	0	64	1.3
C82-85	202–202.9 200–200.9	Non-Hodgkin's	3	5	10	10	12	7	8	5	2	3	65	1.3
C90	203–203.8	Multiple myeloma	1	0	5	3	8	3	0	3	1	0	24	0.5
C92	205–205.9	Myeloid leukemia	4	3	7	6	5	7	3	3	1	2	41	0.8
Women														
C00-C97	140–208.9	all cancer	229	291	386	483	513	539	478	296	121	37	3373	100.0
C15	150–150.9	Esophagus	0	1	1	4	4	5	5	5	0	0	25	0.7
C16	151–151.9	Stomach	32	49	59	83	104	103	96	63	35	6	630	18.7
C18	153–153.9	Colon	10	35	44	54	53	67	59	41	12	6	381	11.3
C19-20	154–154.9	Rectum	15	15	24	25	29	28	27	11	10	2	186	5.5
C22	155–155.9	Liver and intrahepatic bile ducts	5	14	22	31	38	43	29	11	8	2	203	6.0
C23	156	Gall bladder	0	3	3	3	5	5	4	6	0	0	29	0.9
C24	156.1–156.9	Other and unspecified parts of biliary tract	2	3	5	8	12	21	16	13	5	2	87	2.6
C25	157–157.9	Pancreas	3	6	9	26	25	35	28	19	5	1	157	4.7
C33-34	162–162.9	Lung	16	8	26	42	52	56	60	34	10	5	309	9.2
C50	174–175.9	Breast	72	74	71	73	58	42	30	13	6	0	439	13.0
C53	180–180.9	Cervi uteri	16	17	8	22	15	14	17	8	1	0	118	3.5
C54	182–182.9	Corpus uteri	9	13	22	15	7	8	4	0	0	0	78	2.3
C55	184–184.9	Uterus, part unspecified	0	0	1	1	2	3	1	1	2	0	11	0.3
C56	183–183.9	Ovary	15	13	18	12	8	10	12	7	4	0	99	2.9
C64	189–189.1	Kidney	2	1	4	3	2	2	5	1	3	0	23	0.7
C65-67	189.2–189.4	Urothelial tract	0	0	4	3	5	7	3	3	0	1	26	0.8
C82-85	200–200.9 202–202.9	Non-Hodgkin's	2	3	4	10	7	6	6	5	4	1	48	1.4
C90	203–203.8	Multiple myeloma	0	0	3	4	4	4	6	3	1	1	26	0.8
C92	205–205.9	Myeloid leukemia	4	5	3	4	3	6	1	2	0	0	28	0.8

1.22 among women. The SMR of all causes was 0.91 among men and women, and the SMR of all cancers was 1.02 among men and 0.97 among women. Stomach cancer was the most frequent cancer among men (25.5%) and women (18.7%), followed by lung cancer among men (17.1%) and breast cancer among women (13.0%) (Table 5). The leading cause of death was cancer among men (35.0%) and cardiovascular disease among women (41.0%), and the second-leading cause of death was cardiovascular disease among men (33.0%) and cancer among women (25.7%) (Table 6). Among those who died of cancer, the first-, second-, and third-leading causes of death were cancer of the lung (21.9%), stomach (21.2%), and liver (14.4%) among men, and cancer of the stomach (18.7%), colon/rectum (13.2%), and lung (11.8%) among women.

Discussion

The Three-Prefecture Cohort Study, which had approximately 100,000 participants with consecutive follow-up for up to 15 years and a 90% response rate to the baseline questionnaire survey regarding participants' lifestyles, was one of the largest representative prospective, population-based cohort studies in Japan. The study areas were selected because they contained national air monitoring stations and the community-based cancer registry was conducted actively; this large-scale observation enabled us to determine not only all-cause mortality but also cancer incidence among community residents. The association of air pollution and lung cancer mortality was reported previously.[6] This report briefly describes the characteristics (e.g., smoking status, alcohol drinking status, and type of occupation) and endpoints among study participants by gender.

This study had several strengths. First, more than 100,000 participants answered a baseline questionnaire survey, and the response rate was approximately 90%. This response rate was similar to those of the JACC Study, which was launched in the mid-1980s,[1] and the JPHC Study, which was launched in the 1990s.[2] Many cohort studies in Japan have focused on residents in rural areas in order to conduct long-term follow-up.[1,2] However, since this study included both urban and rural areas, findings from this cohort may help to evaluate the relationship between lifestyles and various diseases, irrespective of area. This study population was similar to the general population in cancer and mortality risks, with SIR and SMR close to 1.0.[11,12] Considering the large sample size, the high questionnaire response rate, and adequate regional balance, we consider that the association between participants' lifestyles and endpoints measured in this study is generalizable to the whole population of Japan. Second, in contrast to other large-scale cohorts in Japan, the collection of detailed information on participants' occupation, such as the longest period of employment, is another strength of this study, and we will address the association between occupation and incidence and mortality of non-communicable

Table 6
Distribution of number of deaths by cause, gender, and age at baseline during 15-year follow-up.

ICD10	ICD9		Age at baseline, years										Total	%	%
			40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85			
Men															
All causes			320	506	960	1268	1407	1790	2054	1642	850	359	11,156	100.0	
A00-B99	1–139.8	Certain infectious and parasitic diseases	22	11	38	40	31	46	35	28	10	6	267	2.4	
C00-C97	140–208.9	all cancer	135	230	463	642	615	641	626	375	140	35	3902	35.0	100.0
C15	150–150.9	Esophagus	15	13	22	41	32	27	26	9	7	0	192		4.9
C16	151–151.9	Stomach	28	39	104	126	120	137	151	84	29	11	829		21.2
C18	153–153.9	Colon	10	17	38	40	41	47	33	30	13	1	270		6.9
C19-20	154–154.9	Rectum	10	10	20	25	27	19	19	19	4	1	154		3.9
C22	155–155.9	Liver and intrahepatic bile ducts	16	52	107	127	80	76	60	29	14	2	563		14.4
C23	156	Gall bladder	0	4	4	4	10	9	6	4	0	1	42		1.1
C24	156.1–156.9	Other and unspecified parts of biliary tract	3	6	11	8	13	21	14	12	5	2	95		2.4
C25	157–157.9	Pancreas	9	14	21	39	41	36	33	23	6	2	224		5.7
C33-34	162–162.9	Lung	22	36	66	123	152	165	171	89	24	8	856		21.9
C61	185–185.9	Prostate	0	4	7	11	20	27	24	16	13	1	123		3.2
C64	189–189.1	Kidney	0	3	3	6	8	8	6	3	0	0	37		0.9
C65-67	189.2–189.4	Urothelial tract	0	0	1	4	2	3	3	1	0	0	14		0.4
C82-85	200–200.9 202–202.9	Non-Hodgkin's	3	2	9	12	11	10	13	8	2	2	72		1.8
C90	203–203.8	Multiple myeloma	1	1	3	2	5	3	2	3	0	0	21		0.5
C92	205–205.9	Myeloid leukemia	3	3	6	5	8	6	4	2	1	2	40		1.0
E00-E89	240–279.9	Endocrine, nutritional and metabolic diseases	0	6	9	14	20	29	19	26	17	3	143	1.3	
G00-G99	330–359.9	Diseases of the nervous system	1	5	6	9	12	18	10	8	3	0	72	0.6	
I00-I99	390–459.9	Diseases of the circulatory system	76	121	242	304	407	578	772	644	364	173	3681	33.0	
I20-I25	410–414.9	Ischemic heart disease	16	33	62	74	116	142	176	115	60	16	810		
I48	427.3	Atrial fibrillation and flutter	0	0	3	2	1	6	7	6	4	2	31		
I50	428–428.9	Heart failure	23	32	48	53	74	107	182	181	94	50	844		
I60-69	430–438.9	Cerebrovascular disease	26	42	87	130	143	216	308	270	166	88	1476		
I71	441–441.9	Aortic aneurysm and dissection	2	2	5	8	15	21	13	8	5	2	81		
J00-J99	460–519.9	Diseases of the respiratory system	4	14	41	76	134	255	351	299	161	59	1394	12.5	
J10-J18	480–487.9	Influenza	1	8	15	46	68	139	228	198	113	40	856		
J43	492	Emphysema	0	0	5	5	5	22	19	14	4	5	79		
K00-K93	520–579.9	Diseases of the digestive system	21	39	63	61	59	69	62	59	27	6	466	4.2	
K74	571.5–571.6	Fibrosis and cirrhosis of liver	7	14	38	26	22	17	12	10	6	0	152		
N00-N99	580–629.9	Diseases of the genitourinary system	4	7	12	29	36	37	57	53	25	8	268	2.4	
N17-N19	584–586	Acute kidney failure and chronic kidney disease	3	7	11	21	32	28	48	43	17	2	212		
R00-R99	780–799.9	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	7	3	5	15	17	33	51	80	67	56	334	3.0	
R54	797	Age-related physical debility	1	0	0	1	1	11	15	57	52	55	193		
S00-T88	800–999.9	External causes	42	56	60	57	53	43	41	35	21	5	413	3.7	
		Others	8	14	21	21	23	41	30	35	15	8	216	1.9	
Women															
All causes			181	301	446	662	946	1365	1712	1648	1157	666	9084	100.0	
A00-B99	1–139.8	Certain infectious and parasitic diseases	6	7	21	24	36	31	38	33	21	4	221	2.4	
C00-C97	140–208.9	all cancer	98	170	211	286	325	410	404	278	115	34	2331	25.7	100.0
C15	150–150.9	Esophagus	0	0	2	6	2	4	8	5	3	0	30		1.3
C16	151–151.9	Stomach	15	29	35	49	51	74	80	65	31	7	436		18.7
C18	153–153.9	Colon	5	16	22	27	25	30	46	33	10	5	219		9.4
C19-20	154–154.9	Rectum	3	10	13	16	13	19	16	10	9	2	111		4.8
C22	155–155.9	Liver and intrahepatic bile ducts	4	14	14	26	40	38	30	11	8	2	187		8.0
C23	156	Gall bladder	1	2	7	9	8	19	15	9	1	0	71		3.0
C24	156.1–156.9	Other and unspecified parts of biliary tract	3	6	8	7	13	21	14	16	7	2	97		4.2
C25	157–157.9	Pancreas	5	6	12	32	25	40	30	18	6	2	176		7.6
C33-34	162–162.9	Lung	11	12	17	36	38	55	57	33	11	5	275		11.8
C50	174–175.9	Breast	23	29	22	16	22	16	11	8	3	0	150		6.4
C53	180–180.9	Cervi uteri	5	4	1	4	7	8	5	4	0	0	38		1.6
C54	182–182.9	Corpus uteri	1	4	4	3	0	3	7	0	0	0	22		0.9
C55	184–184.9	Uterus, part unspecified	0	0	0	1	2	1	1	0	2	0	7		0.3
C56	183–183.9	Ovary	8	9	15	10	8	9	11	6	4	0	80		3.4
C64	189–189.1	Kidney	1	0	0	3	0	1	7	1	3	0	16		0.7
C65-67	189.2–189.4	Urothelial tract	0	0	2	1	4	1	2	0	0	0	10		0.4
C82-85	200–200.9 202–202.9	Non-Hodgkin's	1	2	4	8	9	9	3	6	4	1	47		2.0
C90	203–203.8	Multiple myeloma	0	1	3	4	4	5	8	4	1	0	30		1.3
C92	205–205.9	Myeloid leukemia	2	5	3	4	4	6	1	2	0	0	27		1.2
E00-E89	240–279.9	Endocrine, nutritional and metabolic diseases	2	4	5	12	18	20	37	29	15	3	145	1.6	
G00-G99	330–359.9	Diseases of the nervous system	3	2	8	4	11	13	9	12	4	0	66	0.7	
I00-I99	390–459.9	Diseases of the circulatory system	33	65	112	171	322	543	753	780	600	343	3722	41.0	
I20-I25	410–414.9	Ischemic heart disease	4	9	24	39	73	127	134	123	89	32	654		
I48	427.3	Atrial fibrillation and flutter	0	0	0	2	0	3	7	8	2	1	23		

Table 6 (*continued*)

ICD10	ICD9		Age at baseline, years										Total	%	%
			40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85			
I50	428–428.9	Heart failure	9	8	20	28	71	124	164	218	173	118	933		
I60-69	430–438.9	Cerebrovascular disease	12	33	50	81	130	218	335	337	251	150	1597		
I71	441–441.9	Aortic aneurysm and dissection	1	1	0	1	5	8	12	8	2	0	38		
J00-J99	460–519.9	Diseases of the respiratory system	7	12	20	47	81	111	197	221	138	75	909	10.0	
J10-J18	480–487.9	Influenza	1	4	8	25	44	72	133	149	98	67	601		
J43	492	Emphysema	0	0	0	1	2	1	1	4	3	2	14		
K00-K93	520–579.9	Diseases of the digestive system	9	9	24	39	38	62	68	68	54	26	397	4.4	
K74	571.5–571.6	Fibrosis and cirrhosis of liver	5	5	10	18	17	22	22	10	2	0	111		
N00-N99	580–629.9	Diseases of the genitourinary system	3	3	9	19	23	45	65	52	43	17	279	3.1	
N17-N19	584–586	Acute kidney failure and chronic kidney disease	3	3	8	17	18	33	50	38	29	16	215		
R00-R99	780–799.9	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	2	3	2	11	11	33	51	109	119	141	482	5.3	
R54	797	Age-related physical debility	0	0	0	0	2	16	28	87	112	130	375		
S00-T88	800–999.9	External causes	11	18	15	31	50	52	46	26	21	11	281	3.1	
		Others	7	8	19	18	31	45	44	40	27	12	251	2.8	

diseases in the future using this cohort data. Third, the use of community-based cancer incidence data from a cohort of 100,000 participants was also a strength of this study, because there are few available analyses of cancer incidence data from large-scale cohort studies in Japan. Fourth, this cohort can be pooled with other large-scale cohorts in Japan (e.g., the JACC Study,[1] the JPHC Study,[2] or the Ohsaki Cohort[13]) and serve to provide new findings from Japan.

This study has several limitations. First, this registry was launched in the 1980s and its follow-up of participants was completed in 2000. The associations between participants' lifestyles and endpoints might differ from those since 2000, because lifestyles diversify with the times. Second, in cohort studies, non-questionnaire responders had more unfavorable lifestyles than responders[2,14–16] and were less likely to join the health check-ups.[2] However, the overall response rate in this cohort was almost 90%, and we consider that the impact of differences between responders in cities and those in towns would be small. Furthermore, the numbers of delivered questionnaires in Sendai City and Osaka City were fewer than those in other cities/towns, because residents' local organizations did not cover the entire community and could not deliver questionnaires in the whole region. Therefore, the representativeness would be weaker in these areas than in other areas. Third, we could not evaluate the energy intake or nutrient consumption of participants because the Three-Prefecture Cohort Study used a food frequency questionnaire with a small number of items.

Conclusions

The Three-Prefecture Cohort Study was conducted from the 1980s to 2000 and is one of the largest representative prospective population-based cohort studies in Japan. This study enabled us to reveal the association of multiphasic lifestyle factors with cancer incidence and mortality in a single cohort. It will also allow us to conduct a pooled analysis in combination with other large-scale cohorts, which will be of considerable help in gaining insights into the epidemiology of non-communicable diseases in Japan.

Conflicts of interest

None declared.

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