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## INTRODUCTION - METHODOLOGY

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### Selection of Cases and Controls for the Nested Case-control Study within the JACC Study: the First-wave

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#### Abstract

In this paper, we describe the methodology of the case and control selection for the first-wave nested case-control study within the JACC Study. Among the subjects participating in the cohort, serum samples of 42,249 subjects (including 39,242 subjects aged between 40 and 79 at the baseline) were suitable for biochemical analysis. We here selected those who had died by 1997 or who were diagnosed with cancer with sera until 1994 as cases. For each case, 3 to 4 controls with sera were randomly selected, with matching for gender, age (as near as possible) and residential area. As a result, 3,144 cases and 10,661 controls (2,867 cases and 10,351 controls were 40 to 79 years old at the baseline) were selected to measure serum IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1 and sFas values and total SOD activity. Cases were older and more likely to be men than the JACC Study subjects. Moreover, they were much older than controls because of the age-dependence of susceptibility to death, especially among men. There were more smokers among cases compared with controls, though drinkers at the baseline were fewer. Among deceased cases, cancer was the leading cause of death, followed by cardiovascular diseases. Lung cancer was most frequent among deceased cancer cases and the next most common site was the stomach. The leading cause of cancer incidence was stomach cancer followed by lung cancer. Simple comparison of means and distribution of IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1, sFas and total SOD activity between cases and controls revealed total SOD activity and sFas levels of cases to be higher than controls, while for the other components the opposite was found.

**Keywords:** Japan Collaborative Cohort Study - nested case-control study - cancer mortality and incidence

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#### Introduction

Much cancer prevention research has focused on molecular biology related to cytokines or other particular molecules associated with the promotion or inhibition of the development of carcinogenesis and apoptosis. With stocked sera from the Japan Collaborative Cohort Study (JACC Study), we therefore decided to measure some components (insulin growth factor (IGF)-I, IGF-II, IGF-binding protein 3 (IGFBP-3), transforming growth factor (TGF)- $\beta$ 1, soluble Fas (sFas), and total superoxide dismutase (SOD) activity), primarily to evaluate relations to cancer incidence or mortality in the late of 1990s. This was the first-wave nested case-control study within the JACC Study, and thereafter, site-specific nested case-control studies were also planned to evaluate relationship between other biological markers and cancer (Ito et al.,

2003; Ozasa et al., 2004; Suzuki et al., 2004; Yatsuya et al., 2004; Ito et al., 2005a; 2005b; Kojima et al., 2005; Ozasa et al., 2005a; 2005b; Tamakoshi K et al., 2005; Wakai et al., 2005; Fujita et al., 2006; Suzuki et al., 2006).

We have already published findings for relationships between all cancers or some cancer sites and serum levels of IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1 and sFas or total SOD activity (Wakai et al., 2002; Lin et al., 2004; Yatsuya et al., 2005a; 2005b; Lin et al., 2006; Pham et al., 2007a; 2007b; Tamakoshi et al., 2008; Lin et al., 2009) measured in the first-wave.

While the methods for assessment of these components were already described elsewhere (Ito et al., 2005c), the methodology for the case and control selection was not formally explained. Thus, this is the focus of the present paper concerning the first-wave nested case-control study within the JACC Study.

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## Methods

The JACC Study was conducted from 1998 to 1990, involving subjects living in 45 municipalities, across Japan. Details of its cohort design and methods were previously described (Ohno et al., 2001; Tamakoshi A et al., 2005).

At baseline in 37 areas, the cohort participants donated blood samples, and serum of each participant was divided into 3 to 5 tubes (100 to 500  $\mu$ L per tube). They were stored in deep freezers at  $-80^{\circ}\text{C}$  until 1999. The proportion of blood donation to the whole JACC Study subjects was approximately 35%. Prior to the measurement of serum components, the condition of all sera were macroscopically examined, and we found that serum samples of 42,249 participants (including 39,242 subjects aged 40 to 79 at the baseline) were suitable for biochemical analysis.

The JACC Study established a working group to select components to be measured in the first-wave nested case-control study. From the point of view of cancer prevention research, cytokines, proteins, minerals and special molecules associated with the promotion or inhibition of the development of carcinogenesis and apoptosis were nominated to be measured. Finally, the following serum components were selected as they are stable with long-term refrigerated storage: IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1 and sFas, as well as SOD activity. The study design and use of serum were approved by the Ethical Board at the Nagoya University School of Medicine, where the central office of the JACC Study was located at the time.

**Table 1. Characteristics of the Selected Cases and Controls (aged 40-79 at the baseline)**

	Men			Women		
	Cases	Controls	All	Cases	Controls	All
Total Number	1,497	5,388	46,465	1,370	4,963	64,327
Age distribution*						
40-49	3.7	5.3	25.4	8.5	8.5	24.1
50-59	16.8	22.1	30.2	22.2	21.4	31.0
60-69	42.9	53.0	30.0	40.2	43.3	30.6
70-79	36.6	19.5	14.4	29.1	26.8	14.3
Mean	65.8	63.0	57.6	63.7	63.5	57.9
SD	8.2	7.6	10.2	9.2	8.9	10.1
Residential area*						
Hokkaido	5.6	6.0	3.2	4.2	4.3	3.5
Tohoku	21.0	21.4	13.4	17.2	17.1	13.7
Kanto	14.0	16.0	9.5	10.9	13.1	8.9
Chubu	22.0	21.5	33.8	20.4	18.7	28.2
Kinki	21.0	21.2	17.2	17.1	17.4	15.8
Chugoku	8.1	5.3	11.0	14.5	12.8	14.9
Kyushu	8.4	8.6	12.0	15.7	16.6	15.1
Smoking status*						
Current	54.2	47.5	50.5	5.5	2.7	4.8
Quitter	27.9	27.5	25.1	2.1	1.6	1.5
Non-smoker	13.6	21.1	19.5	81.8	86.4	80.1
Drinking status*						
Current	65.7	71.1	71.6	18.8	19.1	22.1
Quitter	9.4	5.2	6.1	1.6	1.0	1.5
Non-drinker	20.3	20.3	17.9	72.5	73.9	66.8

\*Percentage data. Totals are not 100% because of missing values (smoking and drinking status)

The causes and dates of death among the study subjects were determined by reviewing all death certificates in each study area with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications) till 1997. Participants who had moved out from their study areas at baseline were also identified in each area by reviewing the population-register sheets of cohort members. Cancer incidences, including primary cancer site, histological category, and date of incidence were also identified in 24 areas out of 45 until 1994.

Those who had died by 1997 or who had suffered from cancer by 1994 with sera were regarded as cases for our first-wave nested case-control study. For each case, we randomly selected 3 to 4 controls with sera, matching them for gender, age (as near as possible) and residential area. For this first-wave nested case-control study, 2 tubes of each subject were used to measure serum levels of IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1, sFas and total SOD activity. Measurements methods were described elsewhere (Ito et al., 2005c). Distribution and means of these components among cases and controls were compared.

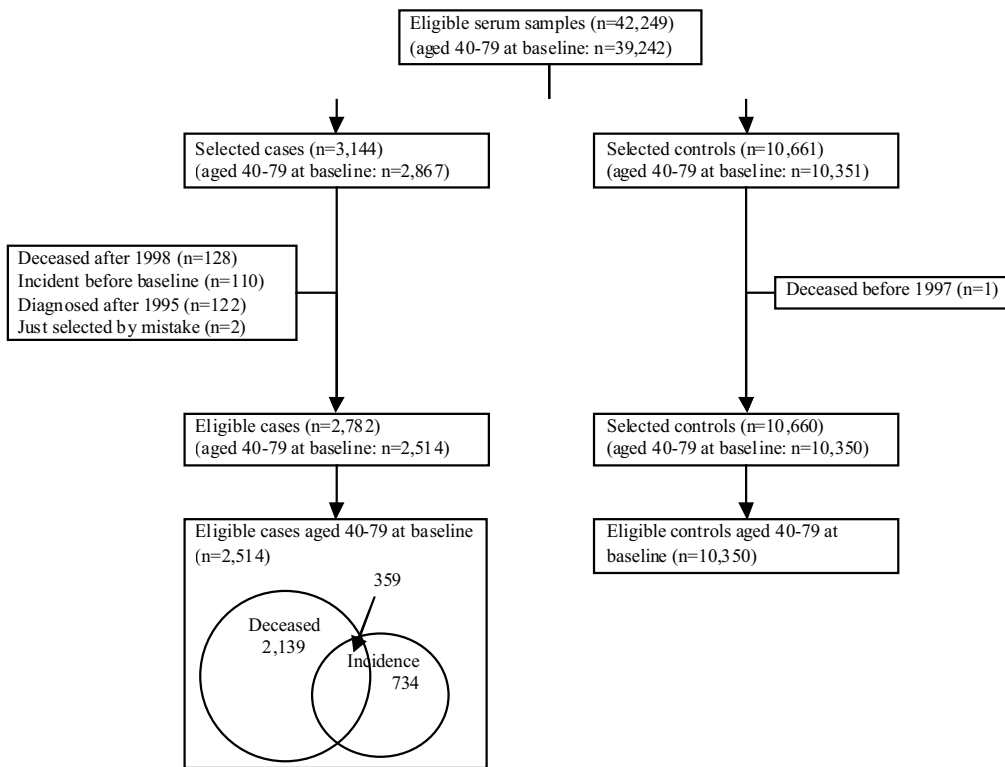
## Results

According to the criteria, 3,144 cases and 10,661 controls (2,867 cases and 10,351 controls were 40 to 79 years old at the baseline) were selected, and their serum IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1, sFas values and total SOD activity were measured. Some characteristics of selected cases and controls comparing with the whole JACC Study subjects are shown in Table 1. Cases were elder and more likely to be men than the whole JACC Study subjects, as they were consisted from deceased or cancer incident cases. Because some area did not stock sera, the distribution of residential areas was not

**Table 2. Causes of Death and Incident Cancer Sites of Selected Cases (age 40-79 at the baseline)**

Total Dead Cases	2,139	100.0
Cancer deaths	950	44.4 (100.0)
Stomach	180	(18.9)
Colon	67	(7.1)
Liver and intrahepatic bile ducts	85	(8.9)
Pancreas	69	(7.3)
Bronchus and lung	197	(20.7)
Cardiovascular diseases	578	27.0
Respiratory diseases	176	8.2
External causes	181	8.5
Others	254	11.9
Total Cancer Incident Cases	734	100.0
Stomach	191	26.0
Colon	77	10.5
Liver and intrahepatic bile ducts	49	6.7
Bronchus and lung	79	10.8
Breast	49	6.7
Others or unknown	265	36.1
Benign tumor	24	3.3

Three hundred and fifty-nine cases were grouped into both (dead cases and cancer incident cases).



**Figure 1. Flow Chart for Selection of Cases and Controls**

comparable between cases and the whole cohort. However, between selected cases and controls, distributions of the matching factors, such as gender and area were similar. Among men, cases were much elder than controls, because elder subjects were more likely to be die than younger, however, unfortunately there were not enough elder subjects with sera to be selected as controls. As a result, frequency matching pattern was difficult to keep for men’s age distribution. There were more smokers among cases compared with controls, though drinkers at the baseline were lesser.

After the measurement, we found some misclassified

**Table 3. Distribution of Serum Components among Cases and Controls (age 40-79 at baseline)**

	N	Mean ± SD	Percentile points		
			25%	50%	75%
<b>IGF-I (ng/ml)</b>					
Cases	2,514	121.8 ± 56.0	87	120	150
Controls	10,346	125.7 ± 55.7	91	120	160
<b>IGF-II (ng/ml)</b>					
Cases	2,514	563.6 ± 144.7	470	560	650
Controls	10,346	586.8 ± 124.3	510	580	660
<b>IGFBP-3 (µg/ml)</b>					
Cases	2,514	2.849 ± 0.889	2.23	2.79	3.37
Controls	10,346	2.981 ± 0.800	2.43	2.92	3.46
<b>TGF-β1 (ng/ml)</b>					
Cases	2,497	34.96 ± 9.09	29.3	34.6	40.5
Controls	10,309	36.25 ± 8.52	30.6	35.9	41.5
<b>sFas (ng/ml)</b>					
Cases	2,496	2.57 ± 2.57	1.9	2.3	2.8
Controls	10,301	2.34 ± 2.03	1.8	2.2	2.6
<b>SOD (U/ml)</b>					
Cases	2,514	3.45 ± 2.62	2.3	2.7	3.3
Controls	10,350	3.36 ± 2.63	2.3	2.6	3.1

cases and a control included. The reasons were as follows: deceased after 1998 (128 cases), incident before baseline (110), diagnosed after 1995 (122) and just selected by mistake (2) for cases, and deceased before 1997 (1 control) for a control. Thus, 2,782 cases and 10,660 controls left, and those aged 40 to 79 at the baseline were 2,514 (90.4%) and 10,350 (97.1%), respectively (Figure 1). Among these 2,514 cases, 2,139 (85.1%) were deceased and 734 (29.2%) were incident cancer sufferers including 24 benign tumor, while 359 were grouped into both because they were firstly registered as cancer incident cases and thereafter died till 1997. Among deceased cases, cancer was the leading cause and the following was cardiovascular diseases (Table 2). Most frequent site observed was lung and the next was stomach among cancer mortality cases. In contrast, the leading cause among incident cases was stomach cancer followed by lung cancer.

Table 3 indicated distribution of measured components among eligible cases and controls aged 40 to 79 at the baseline. Means of sFas levels and total SOD activity were higher among cases compared with controls, whereas others were higher among controls.

**Discussion**

Within the JACC Study, we here selected 3,144 cases and 10,661 controls (2,867 cases and 10,351 controls were 40 to 79 years old at the baseline) to evaluate risks of some serum components to mortality from all-causes, all cancers, site-specific cancers or cancer incidences. Cases and controls were well matched on their frequency of gender and area, however, age distribution was biased because of susceptibility to death of elderly especially

among men. Simple comparison of means and distribution of IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1, sFas and total SOD activity between cases and controls indicated that sFas levels and total SOD activity of cases were higher than controls whereas other components were opposite.

There is one issue we have to keep in mind when interpreting the results from our nested case-control studies or cross-sectional studies on controls. Our controls were selected from the subjects who survived at least 7 years (till 1997) and were free from cancer for at least 4 years (till 1994) from the baseline survey. Thus, they might be healthier than the general population, and this may be related to a potential bias.

With this set of cases and controls within the first-wave nested case-control study, we have examined the relationship between serum levels of IGF-I, IGF-II, IGFBP-3, TGF- $\beta$ 1, sFas and total SOD activity and all-cancer or site-specific cancer mortality. Part of the results are documented in the present series of papers.

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