ORIGINAL CONTRIBUTION

Reproductive Life History as Gastric Cancer Risk for Females : Case-Control Study

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The purpose of this study was to investigate whether the reproductive life history, including hormonal environment, was a risk factor for gastric cancer in females by age groups or by histological subgroups. A case-control study with incident cases accompanied by individually matched one or two controls was carried out, using self administered questionnaire which included personal profile, smoking and drinking habits, dietary habits, past history of disease and reproductive life history. Analysis was made for 116 females cases and matched 144 controls separately by two histological type subgroups (differentiated and undifferentiated type) and by two age groups (young and older), using proportional hazard model to obtain relative risks with 95% C.I. For the undifferentiated gastric cancer in female under 40 years of age, mean of cumulative estradiol concentration (CEC) during all pregnant period and mean pregnant period per pregnancy revealed increased relative risk (R.R.) of 7.7 (95% C.I. : 1.41-41.75) (for each 1 ng/ml) and 3.1 (95% C.I. : 1.01-9.55) (for each 10 weeks), respectively. In the same group, 4 bowls or more rice consumption per day and drinking showed significant protective effect (R.R. : 0.20, 95% C.I. : 0.04-0.90 and R.R. : 0.23, 95% C.I. : 0.07-0.70, respectively). For differentiated gastric cancer in both age groups and undifferentiated one in older female, these factors stated above have no striking effect for gastric cancer occurrence. For differentiated type, several dietary habits were suggested to be risk factors for gastric cancer, although they were not statistically significant. On the other hand, for undifferentiated type, this tendency was not observed. This study suggests that etiologic factors for gastric cancer might be differed between histological types, and that undifferentiated type gastric cancer in young female with pregnancy has some etiological relation with reproductive histories.

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Griffis pointed out that the sex ratio of age specific gastric cancer mortalities among younger people is smaller than that among older people in all countries wherever gastric cancer mortalities are either high or low. That is, the mean of sex ratios in the younger group (younger than 40) is under 1.5, but that in the older group (between 50 and 59) is over 2.0¹⁾. Reproductive activities of young females, especially pregnancy, have been considered to be related to this phenomenon^{1,2)}. One of the authors (T.Y.) suggested that lower age at the first pregnancy or at the first birth and higher age at the menarche were the risk factors of gastric cancer in young female³⁾.

Furukawa and his colleagues suggested that estradiol and pregnancy might increase risk of undifferentiated type gastric cancer in young females based on their experiments of rat^{4,5)}. But, no report had considered the length of pregnancy and the dose of estrogens in the relation with the gastric cancer risk in human being, though estrogens were considered to be related factors for gastric cancer^{2,4-7)}. In the present study, it was intended to clarify whether the reproductive life history is a gastric cancer risk for females, using semi-quantitative variables for estrogens based on detailed information of reproductive histories.

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MATERIALS AND METHODS

Study subjects

Cases were histologically confirmed female gastric cancer incident patients aged less than 40 (young), and aged fifties (50-59) (older), admitted at 12 departments of surgery and 1 department of endoscopy in 11 large hospitals in Fukuoka prefecture, Japan, from the first day of 1986 through the last day of 1988. Ages of cases were defined based on the day of the first visit. Histological types of cases were classified into two categories, differentiated and undifferentiated, according to Hanai's criteria⁹⁾ based on the histological diagnosis determined at the pathological department in each hospital using resected or biopsied specimens.

In the young group, two controls for each index case were chosen in order to increase the power of the study because the number of young cases was expected to be small. Controls were chosen from inpatients of the same hospital matched by date of birth (within two years), sex, ward of the hospital and the date of admission to the hospital (within two months). Patients with malignant neoplasms and endocrine diseases were excluded from the controls. When more than two patients were satisfied with the selection criteria of controls, two with the nearest birth date to the index case were selected as controls.

In the older group, one control was selected for each case, using the same selection criteria as in the young group.

The cases and controls chosen were requested to complete the self-administered questionnaires, while in the wards or after discharge. Controls were chosen and surveyed soon after or at the same time as the cases were surveyed.

The questionnaire consists of personal profile, smoking and drinking habits, dietary habits, past history of disease, and detailed reproductive life history.

Analysis

To estimate exposure to estradiol, the variable named 'cumulative estradiol concentration (CEC)' was introduced by calculating the area under the estradiol concentration curve in each reproductive stage, that is the usual menstrual cycle and the pregnant stage, using Hertogh's data⁹⁾. CEC is expressed as follows.

$$\text{CEC (cumulative estradiol concentration) ng} \cdot \text{w/ml} = \int_{\text{age at the menarche}}^{\text{age at the first visit to the out patient clinic}} f(x) dx$$

Where $f(x)$ expresses time depending estradiol concentration. Time (x) is measured by week of menstrual cycle or of pregnancy course. Unit of the CEC is expressed with 'concentration (ng/ml) multiplied by week (w)' as 'ng · w/ml'.

$$f(x) = \begin{cases} 0.06x-0.02 & (\text{for 0-8 week in each pregnancy}) \\ 0.48x-3.59 & (\text{for 9-22 week in each pregnancy}) \\ 0.52x-2.34 & (\text{for over 22 week in each pregnancy}) \\ 0.11x & (\text{for ordinal menstrual cycle, total}) \end{cases}$$

Direct estimate of estradiol exposure for the subject should be expressed by CEC, blood volume and turn over cycle. In the present study, however, blood volume and turn over were assumed to be constant among females studied. Therefore, CEC was adopted as a surrogate of direct estimate of estradiol exposure. Estradiol concentration were cumulated only during pregnancy for 'total CEC during all pregnant period', and total CEC during all pregnant period was divided by total weeks of pregnancy ('Total pregnant period') for 'mean CEC during all pregnant period'.

Total pregnant period, mean pregnant period per pregnancy, total CEC during all pregnancy and mean CEC during all pregnant period were calculated for only female with pregnancy.

For the analysis of dietary, drinking and smoking habits,

Table 1. Histological diagnosis of differentiated and undifferentiated gastric cancer cases.

Diagnosis	No. of Cases	%
Differentiated type	40	
Papillary adenocarcinoma	1	0.9
Well differentiated tubular adenocarcinoma	9	7.8
Moderately differentiated tubular adenocarcinoma	13	11.2
Moderately differentiated adenocarcinoma	8	6.9
Tubular adenocarcinoma	1	0.9
Mucinous adenocarcinoma	2	1.7
Differentiated adenocarcinoma	6	5.2
Undifferentiated type	76	
Poorly differentiated carcinoma	62	53.4
Signet-ring cell carcinoma	14	12.1
Total	116	100.0

Table 2. Number of cases and referents according to case's histological types.

Histological types	Young		Old		Total	
	case	control	case	control	case	control
Differentiated	9	16	31	31	40	47
Undifferentiated	29	50	47	47	76	97
Total	38	66	78	78	116	144

the relative risks were calculated according to dichotomous variables. For the factors concerning to the reproductive life history, means were calculated by age and histological type for cases and controls respectively. Then, paired t-test was done to see the differences between cases and controls.

Relative risks were calculated using the conditional logistic regression method with PHREG on SAS, based on the proportional hazard model by Cox⁽¹⁰⁾.

Analysis was done separately in four subgroups based on age, and two histological types.

RESULTS

Among the female patients admitted to the hospitals during the study period, 202 patients (young: 65, older: 137) with gastric cancer satisfied the criteria for caseness. Of these patients, 33 cases were excluded because of poor health condition or death. Then, 169 cases (young: 55, older: 114) were requested to complete the questionnaire. Among them, 127 cases (young: 41, older: 86) returned questionnaire (Return rate: 75.1%). Among these 127 cases, 116 subjects, who had filled out the questionnaire satisfactorily and had suitable controls who satisfied the matching criteria mentioned above, were used for analysis. Of these 116 cases, 38 were young and 78 were older. Number of case series by histological type are shown in Table 1.

Number of controls who had been selected and surveyed

were 259. Among them, 187 possible controls returned the questionnaire (Return rate: 72.2%). Of these 187, 144 controls both with questionnaire satisfied and with their index cases were analyzed. The number of cases and controls analyzed are shown in Table 2 by histological type of cases. Disease distribution for controls are shown in Table 3.

Daily life habits and past history

Relative risks for daily life habits and past history, and their 95% confidence intervals for each item are shown for the young in Table 4 and for the older in Table 5 by histological type.

In the undifferentiated type of the young group, relative risk for drinking habit (drinker vs. non-drinker) and for rice intake (4 bowls or more a day vs. less than that) were 0.23 (95% C.I.: 0.07-0.70) and 0.20 (95% C.I.: 0.04-0.90), respectively as shown in Table 4. No noticeable relative risks for known risk or preventive factors were shown in this group. In the differentiated type of the young group, relative risks for drinking habit, pickled vegetables, meat products and dairy products seemed to be increased although these were not statistically significant. In this subgroup, relative risks for salty foods and smoked foods were not estimated, but in these case-control sets all cases had consumed these food more than once a day, on the other hand, all controls had not.

In the undifferentiated type in older age groups, the relative risks for pickled vegetables, salty foods, and dried

Table 3. Clinical diagnosis of referents.

Diagnosis according to ICD9		N	%
Infectious diseases	(001-139)	8	5.6
Neoplasms (benign only)	(210-229)	2	1.4
Metabolic diseases	(270-279)	2	1.4
Diseases of the blood and blood-forming organs	(280-289)	3	2.1
Diseases of the circulatory system	(390-459)	8	5.6
Diseases of the respiratory system	(460-519)	4	2.8
Diseases of the gastro-intestinal system	(520-569, 578)	34	23.6
Cholelithiasis	(574)	61	42.4
Diseases of the other digestive system	(570-573, 575-577)	15	10.4
Diseases of the genitourinary system	(580-629)	2	1.4
Diseases of the skin and subcutaneous tissue	(680-709)	1	0.7
Diseases of the musculoskeletal system	(710-739)	1	0.7
Check-up	—	3	2.1
Total		144	100.0

Table 4. Relative risks for gastric cancer by histological subgroups among young females.

Factor	Definition	Differentiated carcinoma			Undifferentiated carcinoma		
		No. of Cases	Relative risk*	95% C.I.	No. of Cases	Relative risk*	95% C.I.
Smoking	Smoker or Ex-smoker/Non-smoker	9	—	—	28	0.73	0.28– 1.92
Drinking	Drinker or Ex-drinker/Non-drinker	9	6.36	0.71–56.94	29	0.23	0.07– 0.70
Rice	4 bowls or more per day/Less than 4	8	0.47	0.04– 5.68	28	0.20	0.04– 0.90
Noodles	Several a week or more/Less than that	8	1.00	0.09–11.03	29	1.40	0.46– 4.30
Consumption of the soup of the noodles	Almost all/Less than that	8	1.00	0.05–18.92	29	0.46	0.10– 2.19
Bread	5 times per week or more /Less than 5	5	0.62	0.06– 7.00	18	0.67	0.19– 2.38
Pickled vegetables	Once a day or more/Less than once	8	4.00	0.36–44.12	29	0.78	0.32– 1.93
Salty foods	Once a day or more/Less than once	8	—	—	28	1.43	0.27– 7.48
Miso soup	Once a day or more/Less than once	8	0.47	0.04– 5.68	28	0.89	0.35– 2.29
Dried fish, smoked foods	Once a day or more/Less than once	8	—	—	29	0.48	0.16– 1.45
Broiled fish	Once a day or more/Less than once	8	1.41	0.09–23.57	29	0.85	0.32– 2.26
Meat products	Once a day or more/Less than once	8	4.00	0.41–39.00	29	1.43	0.55– 3.72
Vegetables	Once a day or more/Less than once	8	2.11	0.36–12.21	29	0.74	0.27– 2.02
Edible wild plant	Once a day or more/Less than once	8	—	—	29	2.00	0.13–31.98
Fruits	Once a day or more/Less than once	8	0.22	0.02– 2.12	29	1.15	0.47– 2.80
Milk	Once a day or more/Less than once	8	2.06	0.33–13.05	28	0.88	0.32– 2.40
Dairy products	Once a day or more/Less than once	8	3.77	0.4–35.47	29	1.11	0.37– 3.34
Coffee	Once a day or more/Less than once	8	—	—	23	2.11	0.18–25.27
History of gastric ulcer	Suffered/Not suffered	9	—	—	29	0.55	0.06– 5.39

*Relative risks were calculated using the conditional logistic regression method (Breslow, 1978) with PHREG on SAS (ver. 6.04) based on the proportional hazard model by Cox (1972).

Variables were calculated as binomial variables in the univariate analysis

fish and smoked foods were almost same as unity, as shown in Table 5. However, in the differentiated type in older age groups, the relative risks elevated above 2 for pickled vegetables, salty foods, and dried fish and smoked foods, although these were not statistically significant.

In all subgroups, gastric ulcer history showed no striking

relative risk. Other diseases in the past were not reported almost at all.

Reproductive histories

In the Table 6 and Table 7, means of the variables related to reproductive life histories were compared

Table 5. Relative risks for gastric cancer by histological subgroups among older females.

Factor	Definition	Differentiated carcinoma			Undifferentiated carcinoma		
		No. of Cases	Relative risk*	95% C.I.	No. of Cases	Relative risk*	95% C.I.
Smoking	Smoker or Ex-smoker/Non-smoker	27	0.57	0.17– 1.95	46	1.50	0.42– 5.32
Drinking	Drinker or Ex-drinker/Non-drinker	28	1.17	0.39– 3.47	44	2.50	0.97– 6.44
Rice	4 bowls or more per day/Less than 4	27	1.33	0.30– 5.96	43	3.33	0.92–12.11
Noodles	Several a week or more/Less than that	27	2.50	0.49–12.89	44	0.33	0.04– 3.21
Consumption of the soup of the noodles	Almost all/Less than that	29	1.00	0.20– 4.96	40	4.00	0.85–18.84
Bread	5 times per week or more /Less than 5	8	—	—	10	—	—
Pickled vegetables	Once a day or more/Less than once	29	3.33	0.92–12.11	42	1.33	0.56– 3.16
Salty foods	Once a day or more/Less than once	28	3.00	0.61–14.86	42	0.71	0.23– 2.25
Miso soup	Once a day or more/Less than once	29	2.00	0.59– 6.79	41	0.80	0.32– 2.03
Dried fish, smoked foods	Once a day or more/Less than once	29	2.25	0.69– 7.31	43	1.13	0.43– 2.92
Broiled fish	Once a day or more/Less than once	27	1.43	0.54– 3.75	44	1.00	0.4– 2.52
Meat products	Once a day or more/Less than once	27	0.71	0.23– 2.25	40	0.44	0.14– 1.44
Vegetables	Once a day or more/Less than once	27	0.56	0.19– 1.66	43	0.78	0.29– 2.09
Edible wild plant	Once a day or more/Less than once	27	1.00	0.06–15.99	42	0.50	0.05– 5.51
Fruits	Once a day or more/Less than once	28	0.83	0.25– 2.73	44	0.90	0.37– 2.22
Milk	Once a day or more/Less than once	29	1.25	0.34– 4.66	40	0.43	0.17– 1.12
Dairy products	Once a day or more/Less than once	27	1.00	0.32– 3.10	40	0.80	0.32– 2.03
Coffee	Once a day or more/Less than once	27	1.00	0.25– 4.00	44	0.80	0.22– 2.98
History of gastric ulcer	Suffered/Not suffered	31	—	—	47	1.00	0.25– 4.00

*Relative risks were calculated using the conditional logistic regression method (Breslow, 1978) with PHREG on SAS (ver. 6.04) based on the proportional hazard model by Cox (1972).

Variables were calculated as binomial variables in the univariate analysis

Table 6. Means and differences of the mean between cases and controls for the measurements concerned with reproductive history by histological group among young females.

Variable	Differentiated					Undifferentiated				
	Case		Control		p*	Case		Control		p*
	N	Mean	N	Mean		N	Mean	N	Mean	
Age (at entry)	9	35.22	16	35.50	0.384	29	35.76	50	35.92	0.364
Age at first marriage	8	23.25	14	26.50	0.063	23	24.22	38	23.84	0.406
Number of pregnancy	9	1.78	15	2.00	0.771	29	2.66	50	2.66	0.874
Number of delivery	9	1.56	15	1.61	0.924	29	2.03	49	1.86	0.483
Age at first pregnancy	7	25.71	10	26.00	0.856	24	25.25	40	24.65	0.343
Age at first birth	6	25.00	8	25.50	0.702	24	25.33	39	24.62	0.230
Age at menarche	9	13.56	14	13.11	0.452	29	13.34	50	12.80	0.036
Menstruation cycle (days)	6	28.67	7	30.17	0.060	20	27.90	28	28.68	0.302
Duration of menstruation (days)	8	5.25	14	5.19	0.944	25	5.84	41	5.83	0.724
Total pregnant period (weeks)**	6	60.83	9	77.92	0.355	19	83.47	29	88.76	0.458
Mean pregnant period per pregnancy (weeks)**	6	31.78	9	36.50	0.497	19	35.27	29	29.29	0.021
Total CEC*** (ng•w/ml)	8	506.95	11	550.93	0.757	24	659.91	37	572.88	0.250
Total CEC*** during all pregnant period (ng•w/ml)**	6	385.08	9	537.84	0.285	19	557.49	29	562.18	0.943
Mean CEC*** during all pregnant period (ng/ml)**	6	5.42	8	6.42	0.488	19	6.64	28	6.00	0.000

*Paired T-test for difference of the mean between cases and controls.

**Only females with pregnancy were analyzed.

***CEC : Cumulative estradiol concentration (roughly estimated indicator for estradiol exposure)

Estradiol concentration were cumulated from the age at menarche to the age at diagnosis for total CEC, only during pregnancy for total CEC during all pregnant period, and total CEC during all pregnant period was divided by total weeks of pregnancy for mean CEC during all pregnant period.

between cases and controls by age and histological types. In undifferentiated type of young group, mean pregnant period per pregnancy and mean CEC (Cumulative estradiol concentration) during all pregnant period were significantly higher in cases than in controls among female with pregnancy. In the same group, age at menarche was higher in the cases with weak statistical significance. In differentiated type among young group, age at the first marriage and menstruation cycle tended to be lower in cases. In the older group, there were no variables with significant difference between cases and controls, as shown in Table 7.

Relative risks of reproductive histories for gastric cancer were shown in Table 8. In the undifferentiated type of the young group, mean CEC during all pregnant period had a statistically significant rise in the risk, 7.7 fold for each unit of the estimated concentration. After adjusted by drinking habit and amount of rice consumption per day, adjusted relative risk for mean CEC during all pregnant period was 12.4 with 95% C.I. 1.45-105.2. Mean of pregnant period also showed relative risk of 3.1. In other subgroups, these elevated risks could not be seen.

The total CEC and the total CEC during all pregnant period did not suggest any risk in all subgroups. Other reproductive histories did not show any obvious risk in all subgroups, neither. Therefore, in the subgroups except

young undifferentiated group, there seemed to be no obvious risk change in reproductive histories.

DISCUSSION

In the present study, information bias should not be serious, because reproductive factors were not to be recognized as risk factors for gastric cancer in general population, and because patients with gastric cancer did not know the histological type of their gastric cancer. Selection criteria for cases and controls seemed not to be related to dietary factors and reproductive factors in the study. Therefore, selection bias might not be important for this study.

Concerning the differences between two histological types, Haenszel et al. analyzed dietary factors in the Japanese in Hawaii dividing cases into two subcategories, following Lauren's criteria, intestinal and diffuse types¹¹. They asserted that salty food consumption showed a higher risk in the intestinal type than in the diffuse type. But in a consequent survey in Japan, they could not find any remarkable differences between the two histological types¹². Buiatti also suggested that the intestinal and diffuse type of gastric cancer had etiologic factors in common¹³.

From the pathological point of view, Lauren¹⁴, Na-

kamura et al.¹⁵⁾ and Sugano et al.¹⁶⁾ compared two histological subgroups of gastric cancer and suggested that two histological type of gastric cancer had different etiology, and Nakamura and Sugano asserted that "undifferentiated type" must be the proper form of stomach cancer^{15,16)}.

No report was appeared on difference of the risk of daily habits between age classes. Kikuchi analyzed only cases of ages of 40 and younger, and concluded that smoking, drinking and obesity were not related with gastric cancer risk, and that gastric cancers occurred in young adults were affected little from environmental factors¹⁷⁾.

In our study, drinking habit and amount of rice per day decreased the risk, 0.23 and 0.20, in undifferentiated type of the young group.

Rice was reported as a risk factor^{11,18,19,20)}. Haenszel found that rice showed higher risk in intestinal type than in diffuse type¹¹⁾. But in some papers, rice had little effect on the gastric cancer^{21,22)}, even when it had been analyzed separately by histological type²³⁾. Drinking habit had been considered as neither risk factor nor protective factor in many papers^{19,22)}, even when it was analyzed individually by histological type²³⁾. Protective effects of drinking habit and rice consumption among undifferentiated type of the young group in this study did not coincide with former

knowledge from studies without analyses by age.

Pickled vegetable, salty and smoked foods, and broiled fish seemed to increase the gastric cancer risk in the differentiated histological type group of both age group, though they were not statistically significant, and fruits seemed to reduce the risk in the same groups, even though it was not statistically significant. These risk factors and protective factors which showed weak effect in this study were all pointed out in former studies as major factors for gastric cancer in general, without consideration of age^{11-13,18-23)}. But, in this study, these factors seemed to be appeared more in differentiated type group than in undifferentiated group, and to effect more in the older females than in the young.

From different distribution of the risk between two histological types presented above, it was suggested that there would be etiologic differences between two histological types when it was analyzed separately by age. Further study should be required to answer this question.

Concerning the reproductive life histories, age at the menarche, mean pregnant period per pregnancy and mean CEC during all pregnant period were significantly higher in cases than in controls only among undifferentiated type of young group. Increased relative risks was also obtained for mean pregnant period per pregnancy and

Table 7. Means and differences of the mean between cases and controls for the measurements concerned with reproductive history by histological group among older females.

Variable	Differentiated					Undifferentiated				
	Case		Control		p*	Case		Control		p*
	N	Mean	N	Mean		N	Mean	N	Mean	
Age (at entry)	31	54.52	31	54.58	0.730	47	54.72	47	54.66	0.722
Age at first marriage	27	23.93	27	22.81	0.329	36	23.83	36	23.61	0.746
Number of pregnancy	28	3.68	28	3.46	0.554	45	3.22	45	3.62	0.273
Number of delivery	27	2.30	27	2.33	0.885	43	2.16	43	2.12	0.851
Age at first pregnancy	25	24.36	25	23.84	0.617	36	25.31	36	24.69	0.521
Age at first birth	24	24.75	24	24.21	0.604	30	24.83	30	24.27	0.539
Age at menarche	28	14.96	28	15.18	0.631	45	14.82	45	14.47	0.376
Menstruation cycle (days)	14	28.50	14	28.86	0.583	24	28.25	24	28.00	0.625
Duration of menstruation (days)	24	5.42	24	5.08	0.466	36	5.25	36	5.61	0.338
Total pregnant period (weeks)**	14	105.07	14	94.29	0.262	14	102.71	14	105.93	0.850
Mean pregnant period per pregnancy (weeks)**	14	30.15	14	33.49	0.157	14	26.01	14	26.29	0.943
Total CEC*** (ng•w/ml)	15	808.17	15	765.18	0.632	15	781.15	15	821.41	0.718
Total CEC*** during all pregnant period (ng•w/ml)**	14	615.80	14	594.42	0.778	14	617.61	14	622.84	0.963
Mean CEC*** during all pregnant period (ng/ml)**	14	5.83	14	6.22	0.387	14	5.24	14	5.46	0.790

*Paired T-test for difference of the mean between cases and controls.

**Only females with pregnancy were analyzed.

***CEC : Cumulative estradiol concentration (roughly estimated indicator for estradiol exposure)

Estradiol concentration were cumulated from the age at menarche to the age at diagnosis for total CEC, only during pregnancy for total CEC during all pregnant period, and total CEC during all pregnant period was divided by total weeks of pregnancy for mean CEC during all pregnant period.

mean CEC during all pregnant period. But, total CEC and total CEC during all pregnancy did not show any increased relative risk, not only in undifferentiated young group but also in other subgroups.

The result that the total CEC and the total CEC during all pregnancy did not show increased risk suggests that the amount of estradiol exposed during her pregnancy or life time did not affect incidence of stomach cancer.

Mean CEC during all pregnant period and mean pregnant period per pregnancy will have maximum value when

all pregnancies of one subject terminated at full term in spite of when number of pregnancy experienced was large. These measures may represent the weight of the pregnancies in later stage among all pregnant period rather than the amount of estradiol exposed through her pregnancy.

In this study, proportion of gallstone disease among controls were very high, 33.3% for the young and 53.8% for the older. Pregnancy and extraneous female sex hormone were thought to be risk factors for gallstone disease.

Table 8. Relative risks of reproductive histories for gastric cancer by histological subgroups among females.

Factor	Definition	Differentiated carcinoma			Undifferentiated carcinoma			
		No. of Cases	Relative risk	95% C.I.	No. of Cases	Relative risk	95% C.I.	
Young females								
Age at menarche	14 y.o. or more/Less than 14	9	1.66	0.36- 7.72	29	1.65	0.62- 4.39	
Age at first marriage	24 y.o. or more/Less than 24	8	0.17	0.02- 1.61	23	2.03	0.60- 6.85	
Number of pregnancy	3 or more/Less than 3	9	0.86	0.13- 5.53	29	0.74	0.31- 1.79	
Number of delivery	3 or more/Less than 3	9	0.78	0.07- 8.88	29	0.92	0.34- 2.48	
Age at first pregnancy	24 y.o. or more/Less than 24	7	1.62	0.14- 18.31	24	2.60	0.71- 9.55	
Age at first birth	24 y.o. or more/Less than 24	6	—	—	24	2.73	0.57-13.06	
Mean pregnant period per pregnancy**	for each 10 weeks	6	0.72	0.25- 2.03	19	3.11	1.01- 9.55	
Total CEC***	for each 100 ng weeks/ml	8	0.95	0.72- 1.25	24	1.09	0.91- 1.30	
Total CEC*** during all pregnant period**	for each 100 ng weeks/ml	8	0.99	0.77- 1.28	24	1.09	0.91- 1.31	
Mean CEC*** during all pregnant period**	for each 1 ng/ml	6	0.88	0.56- 1.38	19	7.68	1.41-41.75	
Older females								
Age at menarche	14 y.o. or more/Less than 14	28	0.71	0.06- 1.38	45	1.50	0.61- 3.67	
Age at first marriage	24 y.o. or more/Less than 24	27	1.00	0.35- 2.85	36	1.10	0.47- 2.59	
Number of pregnancy	3 or more/Less than 3	28	1.25	0.34- 4.66	45	0.70	0.27- 1.84	
Number of delivery	3 or more/Less than 3	27	1.33	0.46- 3.84	43	0.75	0.32- 1.78	
Age at first pregnancy	24 y.o. or more/Less than 24	25	1.00	0.32- 3.10	36	1.13	0.43- 2.92	
Age at first birth	24 y.o. or more/Less than 24	24	2.50	0.49-12.89	30	1.20	0.37- 3.93	
Mean pregnant period per pregnancy**	for each 10 weeks	14	0.35	0.07- 1.69	14	0.97	0.46- 2.07	
Total CEC***	for each 100 ng weeks/ml	15	1.07	0.80- 1.44	15	0.95	0.74- 1.23	
Total CEC*** during all pregnant period**	for each 100 ng weeks/ml	14	1.06	0.72- 1.57	14	0.99	0.77- 1.29	
Mean CEC*** during all pregnant period**	for each 1 ng/ml	14	0.72	0.35- 1.51	14	0.95	0.67- 1.36	

*Relative risks were calculated using the conditional logistic regression method (Breslow, 1978) with PHREG on SAS (ver. 6.04) based on the proportional hazard model by Cox (1972).

**Only females with pregnancy were analyzed.

***CEC: Cumulative estradiol concentration (roughly estimated indicator for estradiol exposure)

Estradiol concentration were cumulated from the age at menarche to the age at diagnosis for total CEC, only during pregnancy for total CEC during all pregnant period, and total CEC during all pregnant period was divided by total weeks of pregnancy for mean CEC during all pregnant period.

Variables were calculated with binomial value other than mean pregnant period per pregnancy, total CEC, total CEC during all pregnant period and mean CEC during all pregnant period. These four variables used with their continuous values, for each 10(weeks) for mean pregnant period per pregnancy, for each 100 (ng weeks/ml) rise for total CEC and total CEC during all pregnant period and for each 1 (ng/ml) rise for mean CEC during all pregnant period.

Estimated total CEC during all pregnant period and mean CEC during all pregnant period were higher in the controls with gallstone disease than those without it among young females. But among older females, these indices were almost equal in both groups. This suggest that the risk differences of total CEC during all pregnant period and mean CEC during all pregnant period would be decreased between cases and controls. Braverman proposed the hypothesis that abnormal gallbladder function in the latter two third of pregnancy contribute to the formation of cholesterol gallstones²⁴). It is similar to become latter two third of pregnancy with that mean pregnant period per pregnancy were longer in the cases in young undifferentiated group, and this suggest that risk difference of the mean pregnant period per pregnancy between cases and controls would be decreased in this study. As mentioned above, high proportion of gallstone disease among controls in this study might arise underestimated risk of pregnancy and related factors.

Some reports concerned reproductive life history on gastric cancer^{3,6,7,13,25}). Yoshimura³) and Tsukuma²⁵) investigated young females. Others treated cases mainly aged over 50. Tsukuma reported that among females of 30 to 34 years of age, relative risk was 0.36 when they had ever been pregnant. Yoshimura didn't found any obviously elevated risk for number of pregnancy or delivery. Among subjects most of whom were aged 50 years or more, Vecchia showed increasing trend of relative risk with number of birth⁷). In that study, they presented discordant effect of oral contraceptive and estrogen replacement, the former showed weak risk and the latter showed weak protective effect⁷). Number of pregnancy and number of delivery (or birth) were assessed in these studies. But, none of these studies concerned about length of pregnant period and evaluated the percentage of delivery among all pregnancies, and none of them analyzed separately by histological type and age.

Concerning the direct effect of estrogens on gastric cancer incidence, Furukawa and his colleagues suggested that estrogens suppressed the induction of gastric carcinoma (mainly differentiated) in male rat, induced by MNNG (N-methyl-N'-nitro-N-nitrosoguanidine)⁴). It was also reported that the number of poorly differentiated stomach region increased in rat which were injected with estrogen⁴). Then, they observed that the incidence of gastric cancer was higher in rats with delivery than in those without pregnancy or in those were resected pregnant uterus and ovaries early in the pregnancy⁵). From these result, they suggested that the sudden decrease of estrogen concentration at delivery might be a factor for increased risk of gastric cancer.

Tsukuma et al. reported that among human females aged 16 to 29, odds ratio had been 5.75 when they had diagnosed gastric cancer within 24 month after the delivery

compared with those who had been diagnosed at 61 month or more after the delivery and suggested that pregnancy affected gastric cancer incidence, but they presented no hypothesis upon the mechanism and didn't analyzed separately by histological type²⁵).

In human females, no report was appeared on gastric cancer, considering hormonal factor itself or length of pregnancies by histological type and by age group. The result of this study suggested that estradiol would not affect on the gastric cancer with hormonal activity of itself, but something in the pregnancy courses would act on initiation or promotion of gastric cancer at least in female with pregnancy in young undifferentiated type. Furukawa's suggestion of the risk increase by the sudden decrease of estrogen concentration at delivery might be one hypothesis for effect of pregnancy on gastric cancer. But, there were no direct evidence in this study that suggested the relation between sudden decrease of estrogen concentration and gastric cancer incidence.

Our study suggested that risk factors for gastric cancer are different between histological types and age classes and that gastric cancers of females may be partly affected by pregnancy and some kind of physiological condition related to pregnancy especially in the undifferentiated histological type of young female with pregnancy. Other epidemiological and experimental studies are expected to clarify the effect of the factors related to pregnancy on gastric cancer risk.

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