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Trends in the Incidence of Female Breast and Cervical Cancers in Miyagi Prefecture, Japan, 1959–1987

Yuko Minami,[1, 3, 4] Akira Takano,[2] Yoshi Okuno,[2] Akira Fukao,[1] Minoru Kurihara[2] and Shigeru Hisamichi[1]

[1]*Department of Public Health, Tohoku University School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980,* [2]*Miyagi Prefectural Cancer Registry, c/o Miyagi Cancer Society, 6-2-81 Kamisugi, Aoba-ku, Sendai 980 and* [3]*Division of Epidemiology, Miyagi Cancer Center Research Institute, 47-1 Nodayama, Medeshima-Shiode, Natori, 981-12*

Trends in the incidence of female breast and cervical cancers were examined, using the cancer registry data in Miyagi Prefecture, Japan, during 1959–1987. The age-standardized incidence rate of breast cancer has been increasing, while that of cervical cancer has been decreasing. Age-period-cohort models were applied to clarify the trends in incidence. For breast cancer incidence, the age-period model adequately represented the data, and demonstrated that the risk of developing breast cancer has been increasing in recent time periods. The effect of cohort on breast cancer incidence was insignificant and the full model containing age, period and cohort showed irregularities in the cohort effect. For cervical cancer incidence, the effect of period was significant, while the effect of cohort was marginal. The full model containing age, period and cohort showed that cervical cancer risk has been decreasing in recent time periods and younger birth cohorts. Using published reports, we investigated the trends in the prevalence of various risk factors and compared them with the trends in the incidence at both sites. It is suggested that the effects of period and cohort might be related to the changes in the prevalence of these risk factors as well as to improvements of the diagnostic procedures.

Key words: Breast cancer — Cervical cancer — Incidence — Time trend — Age-period-cohort model

In recent years, the age-standardized incidence rate of female breast cancer has been gradually increasing, while that of cervical cancer has been decreasing, in Japan. Accordingly, a graph of the age-standardized incidence rates of breast and cervical cancers shows inverse time trends during the last 30 years.[1)]

In the US and the Nordic countries, the trends in breast and cervical cancer age-standardized incidence rates are similar to those in Japan.[2–7)] But, comparing the trends and the patterns in incidence rates between Japan and these western countries in detail, the slopes of the age-standardized incidence rates in the two cancer sites during the last 30 years are larger in Japan, and the shapes of the age-specific incidence curves are different, especially in breast cancer. Age-specific incidence rates of breast cancer after the age of 50 years in Japan decrease or flatten with aging.[8)] Although several studies have reported that the rising breast cancer incidence in the US and Nordic countries might be attributed to a birth cohort effect,[9–11)] such studies in Japan are few.[12)] On the other hand, analyses of the trend in cervical cancer incidence have not been performed in either western countries or Japan.

In the present study, using the cancer registry data in Japan, we investigated the trends in the incidence of breast and cervical cancers and the determinants of such trends. A regression model, an age-period-cohort model, which offers considerable advantages over simple descriptive methods, was applied in this study. The time period effect and the birth cohort effect were disentangled.

MATERIALS AND METHODS

Study population The Miyagi Prefectural Cancer Registry, covering the entire prefecture, was initiated in 1951 and reorganized in 1959. Cases are registered from clinics and hospitals, radiology and pathology departments, autopsy records, mass screening records and death certificates.[13)] Cancer incidence data since 1959 have been stored and reported regularly.

Incidence data of female breast and uterine cancers were obtained by sex and age from the Miyagi Prefectural Cancer Registry for six periods (1959–61, 1962–67, 1968–72, 1973–77, 1978–82, 1983–87). Uterine cancer consists of several subsites; ICD-9 rubric code; 179 (uterus, part unspecified), 180 (cervix), 181 (placenta), 182 (body of uterus) and 2331 (carcinoma *in situ*, uterus). However, as it is likely that most of the part-unspecified uterine cancer cases belong to the leading subsites, i.e., cervix or body, there is a possibility that the

[4] To whom correspondence should be addressed, at the Division of Epidemiology, Miyagi Cancer Center Research Institute.

official cervical cancer incidence rates might be underestimated. Accordingly, the corrected number of cervical cancer cases was calculated using the following equation, and the analyses on cervical cancer were carried out based on this number. *In situ* cases were not included in the analyses:

$$\text{Corrected number of cervical cancer cases} = n1 + n3 \times n1/(n1+n2)$$

where, n1 = number of cases in rubric 180 (ICD-7; 171, ICD-8; 180); n2 = number of cases in rubric 182 (ICD-7; 172, ICD-8; 182.0); n3 = number of cases in rubric 179 (ICD-7; 174, ICD-8; 182.9).

Since the incidence rates of breast and cervical cancers increase rapidly over age 30 and the recent life expectancy of Japanese women is around 80 years,[14] the data for ages 30–79 were used for this study. During the six periods, the percentages of breast cancer cases and the corrected percentages of cervical cancer cases registered from death certificates were each below 10%. The percentages of breast cancer cases verified histopathologically have been increasing (1959; 66.7%, 1987; 95%), while the corrected percentages of cervical cancer cases verified histopathologically have been constant at around 80%.

The incidence data were organized into 10 five-year age groups (30–34 to 75–79 years) and six time periods (1959–61, 1962–67, 1968–72, 1973–77, 1978–82 and 1983–87). Incidence rates by time period were calculated by dividing the mean annual incidence frequency by the mid-year population. From these incidence data, 15 synthetic overlapping birth cohorts (1878–87 to 1948–57) were constructed by combining age and time periods, with treating the incidence rates in 1959–61 and in 1962–67 as those in 1958–62 and in 1963–67, respectively.

To summarize the incidence by time period, direct age standardization to the world population was performed. Age-specific incidence curves by time period and birth cohort are also presented, since graphical presentation may be useful to interpret trends.[15]

Statistical methods To investigate the effects of age, cohort and period on incidence, models were estimated on the assumption that the number of cases constituted a variable with a Poisson distribution. For the analyses, the incidence data were reorganized into six equal 5-year periods (1958–62, 1963–67, 1968–72, 1973–77, 1978–82 and 1983–87). The numbers of cases for 1968–72, 1973–77, 1978–82 and 1983–87 were obtained from the registry and those for 1958–62 and 1963–67 were estimated by using the incidence rates in 1959–61 and 1962–67, respectively. Finally, model fitting was based on 10 five-year age groups and six 5-year time periods and 15 overlapping birth cohorts. As a denominator, person-years for each category were calculated by summing the population counts in the census year and those in the non-census years which were estimated by linear interpolation using the censuses. In the model, it is assumed that each factor has an additive effect on the log rate(λ_{ijk}),[16)]

$$\log\lambda_{ijk} = \mu + \alpha_i + \pi_j + \gamma_k$$

where the age effects are represented by α_i, the period effects by π_j, and the cohort effects by γ_k. The model is fitted by the maximum likelihood method.[17] The statistical significance of each term was tested after making adjustment for the other terms. As age was regarded as an important predictor of the incidence rate, age was taken into account in each model fitting. But, since there are many potential sources of variation in population-based data, the variance in models may be considerably larger than the mean (over-dispersion). In that case, the quasi-likelihood approach[9,18,19] was applied and the F-test was used for the test of statistical significance of each term. The fit of each model was judged based on adjusted R^2_A (adj-R^2_A).[9]

In age-period-cohort models, age, period and cohort are linearly dependent. Namely, when two of them are fixed, the third is also fixed.[20] It is not possible to disentangle the linear effects of all three terms (non-identifiability problem). Therefore, non-linear effects, which can be uniquely defined, were estimated.[9,16,19,21] Year of diagnosis 1958–62 and year of birth 1883–92 were taken as referent categories and relative risks by time period and birth cohort were calculated, respectively. The 95% confidence interval was corrected by the quasi-likelihood approach. However, as the first and last cohorts contain only one cell each and risk estimates are uncertain, the relative risks for these were not presented. Modeling procedure was performed using the GLIM system.[22]

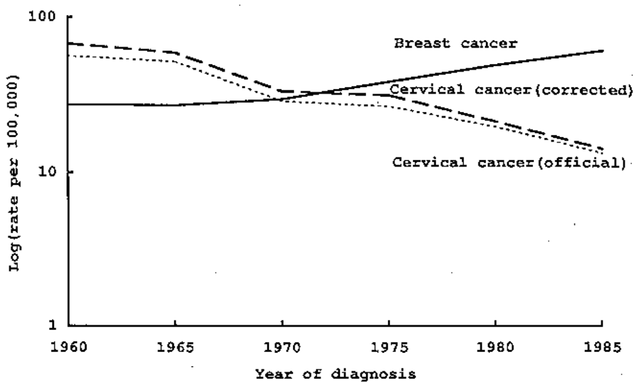

Fig. 1. Trends in age-standardized incidence rates to the world population aged 30–79 during 1959–1987.

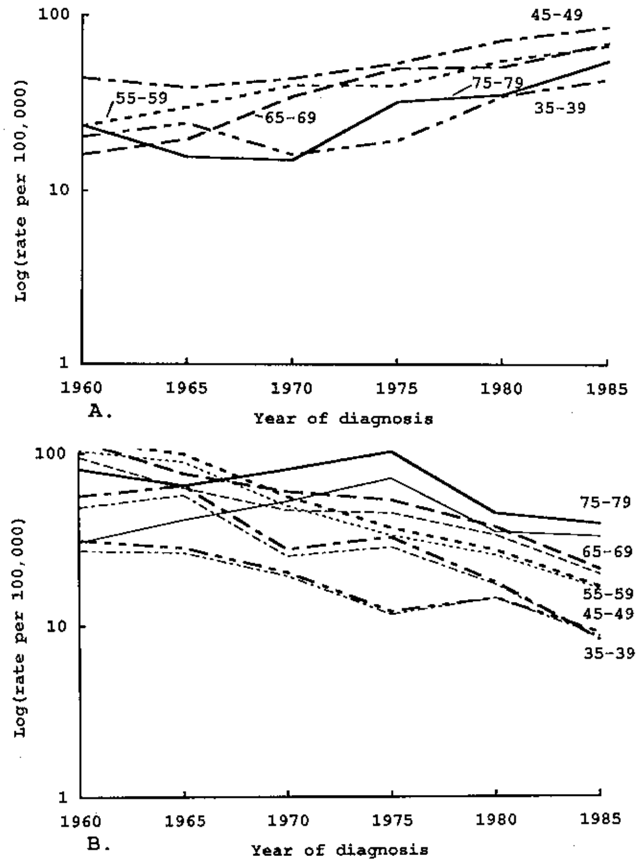

Fig. 2. Trends in age-specific incidence rates by year of diagnosis during 1959–1987. A, breast cancer; B, cervical cancer; thick line, corrected rates; thin line, official rates.

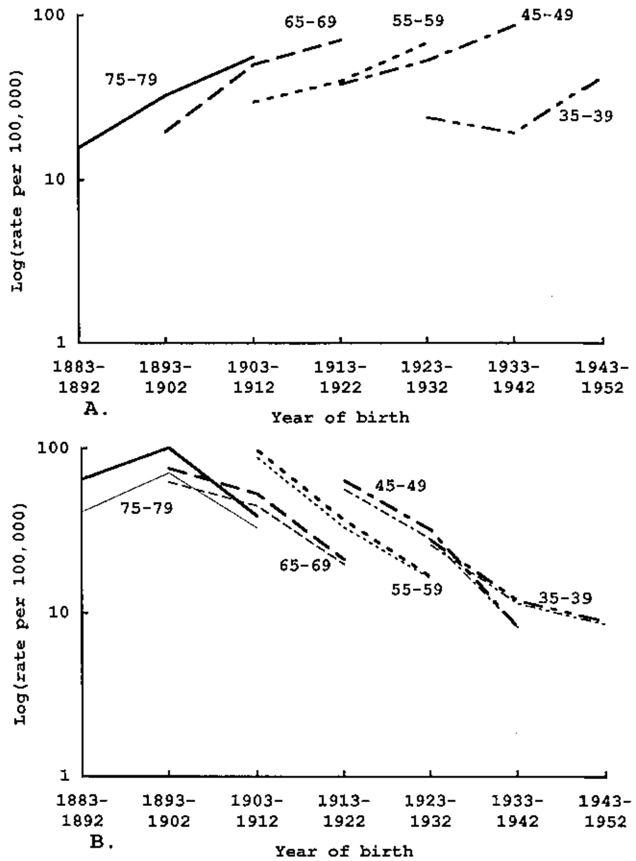

Fig. 3. Trends in age-specific incidence rates by year of birth during 1883–1952. A, breast cancer; B, cervical cancer; thick line, corrected rates; thin line, official rates.

RESULTS

Graphical presentation The trends in age-standardized incidence rates are presented in Fig. 1 on a logarithmic scale. The incidence curves of breast and cervical cancers cross each other at around 1970, showing inverse trends. Fig. 2 and Fig. 3 present the trends in the age-specific incidence rates by time period and birth cohort, respectively. For cervical cancer, both official and corrected rates are presented. The breast cancer incidence rates by time period and birth cohort showed increasing tendencies in all age groups, but the curves were not smooth. The cervical cancer incidence rates by time period and birth cohort decreased in general. However, in the incidence rates by time period, the decreasing tendency in the oldest age group was less marked. The differences between official rates and corrected rates were large in old age groups and earlier periods, indicating the effects of higher rates of part-unspecified uterine cancer in these age groups and periods on cervical cancer incidence.

As a whole, the shapes of graphs are irregular, and it was impossible to disentangle period and cohort effects from the graphical presentation.

Age-period-cohort model The fit of various models to the incidence of breast and cervical cancers is shown in Table I. Age was statistically significant in each model, although the results of statistical testing are not shown. The table is limited to present only the effects of time period and birth cohort. As age-period-cohort modeling revealed some overdispersion in the submodel and full model, statistical test for each term was based on the F-test, taking the value of adj-R^2_A into consideration.

For breast cancer incidence, the addition of period to a model containing age and cohort was statistically significant, while the addition of cohort to a model containing age and period was not. The value of adj-R^2_A for the age-period model (0.86) was higher than that for the age-cohort model (0.79) and was consistent with that for the full model (0.86). Thus, it was considered that the age-period model represented the breast cancer incidence

Table I. Summary Statistics for Age-period-cohort Models of Female Breast Cancer and Cervical Cancer, Year 1958–1987, Aged 30–79 Years

Terms in model	Summary statistics			
	df	Deviance	F-test[a]	adj-R^2_A
Breast cancer incidence				
Age	50	689.15		
Age+Period	45	85.46	0.84	0.86
Age+Cohort	36	102.37	4.84[b]	0.79
Age+Period+Cohort	32	63.78		0.86
Cervical cancer incidence				
Age	50	1487.1		
Age+Period	45	183.60	1.87[c]	0.86
Age+Cohort	36	150.18	3.52[b]	0.86
Age+Period+Cohort	32	104.31		0.89

a) F-statistic of a model refers to a comparison of the submodel with the full model.
b) Statistically significant at $P<0.05$.
c) $P=0.07$.

Table II. Relative Risks of Breast Cancer in Miyagi Prefecture 1958–1987 by 5-Year Period of Diagnosis Based on Age-period Model, and by Year of Birth Based on the Full Model

	Relative risk	95% confidence interval
Year of diagnosis		
1958–1962	1.00	
1963–1967	0.99	0.84–1.18
1968–1972	1.05	0.89–1.24
1973–1977	1.39	1.20–1.62
1978–1982	1.78	1.55–2.06
1983–1987	2.24	1.95–2.57
Year of birth		
1883–1892	1.00	
1888–1897	0.73	0.39–1.37
1893–1902	0.96	0.55–1.69
1898–1907	1.12	0.65–1.95
1903–1912	1.24	0.71–2.19
1908–1917	1.17	0.65–2.12
1913–1922	1.18	0.63–2.22
1918–1927	1.26	0.65–2.46
1923–1932	1.22	0.60–2.50
1928–1937	1.18	0.55–2.52
1933–1942	1.14	0.51–2.56
1938–1947	1.25	0.53–2.96
1943–1952	1.22	0.49–3.06

Table III. Relative Risks of Cervical Cancer in Miyagi Prefecture 1958–1987 by 5-Year Period of Diagnosis and by Year of Birth Based on the Full Model

	Relative risk	95% confidence interval
Year of diagnosis		
1958–1962	1.00	
1963–1967	0.93	0.79–1.09
1968–1972	0.57	0.46–0.70
1973–1977	0.59	0.46–0.77
1978–1982	0.44	0.32–0.61
1983–1987	0.32	0.22–0.46
Year of birth		
1883–1892	1.00	
1888–1897	1.30	0.86–1.98
1893–1902	1.36	0.89–2.06
1898–1907	1.35	0.87–2.08
1903–1912	1.26	0.79–2.02
1908–1917	1.15	0.69–1.93
1913–1922	0.95	0.54–1.69
1918–1927	0.86	0.46–1.60
1923–1932	0.73	0.37–1.44
1928–1937	0.75	0.36–1.57
1933–1942	0.51	0.22–1.17
1938–1947	0.61	0.25–1.50
1943–1952	0.71	0.26–1.90

better than the age-cohort model and that there was no reason to disentangle the effects of the full model.

Table II shows the relative risks by time period obtained from the age-period model and the relative risks by birth cohort obtained from the full model. The relative risks by time period increased markedly and continuously after 1968. However, the relative risks by birth cohort showed irregularities, indicating neither an increasing tendency nor a decreasing tendency. The values of relative risks by time period presented in Table II were similar to those obtained from the full model (data not shown).

For cervical cancer incidence, the addition of period to a model containing age and cohort was statistically significant, but the effect of cohort was marginal when cohort was added to the age-period model (Table I). The

Table IV. Trends in the Prevalence of Various Risk Factors of Breast and Cervical Cancers

Factor	Year							
	1950	1955	1960	1965	1970	1975	1980	1985
Age at menarche (yr.)[a),29)]	Downward trend by 0.11/year until 1966							
Age at first marriage (yr.)[30)]	23.0	23.8	24.4	24.5	24.2	24.7	25.2	25.5
Age at first birth (yr.)[31)]	24.4	24.8	25.4	25.7	25.6	25.7	26.4	26.7
Total fertility rate[32)]	3.65	2.37	2.00	2.14	2.13	1.91	1.75	1.76
Adult height (cm)[33)]	152.7	153.2	153.7	154.8	155.6	156.3	157.0	157.6
Intake of nutrients per capita per day[37)]								
Energy (kcal)	2098	2104	2096	2184	2210	2226	2119	2088
Protein (g)	68	69.7	69.7	71.3	77.6	81	78.7	79
Fat (g)	18	20.3	24.7	36	46.5	55.2	55.6	56.9
Participation rate in breast cancer screening program (%)[a),35)]							3.4	4.8
Participation rate in cervical cancer screening program (%)[a),35)]				5.4	9.5	16.9	20.4	25.1

a) Data in Miyagi Prefecture.

value of adj-R^2_A of the full model (0.89) was larger than those for the submodels (AP model 0.86; AC model 0.86). Furthermore, in age-period and age-cohort models, large residuals were observed around several fitted values. Thus, as the fit of the full model was regarded as better than those of age-period and age-cohort models, the full model was used for summary description. Table III shows the relative risks by time period and birth cohort obtained from the full model. The relative risks by time period decreased markedly after 1968. The relative risks by birth cohort suggest a declining trend, beginning with the cohort in 1898–1907.

DISCUSSION

The analyses of the data from the Cancer Registry of Miyagi Prefecture, Japan, during 1959–1987 revealed significant effects of period on female breast and cervical cancer incidence. Although a linear effect for each term was not estimated on an age-period-cohort model, the relative risk estimates for each category indicate that the trends of incidence are opposite for breast and cervical cancers; the relative risks by time period are increasing for breast cancer, and decreasing for cervical cancer. Furthermore, the effect of cohort on the breast cancer incidence, which was insignificant, showed irregularities. In contrast, the risk for cervical cancer decreased in younger birth cohorts. Although, in western countries, the rising breast cancer incidence is explained chiefly by cohort effects,[9–11)] and Wakai and his colleagues recently reported a increase of breast cancer risk among Japanese women born after 1900,[12)] a steady increase of breast cancer risk with birth cohort was not observed in this study. In Wakai's study, the observation period is 1975–1985, which is shorter than that in ours, and period effects were not analyzed. The inconsistency between this study and Wakai's study is likely to be attributed to this difference in the observation period.

Epidemiological studies of breast and cervical cancers have identified several risk factors for both sites. It is well known that reproductive factors are associated with risks of breast[23–25)] and cervical[26)] cancers. Recent studies reported that dietary factors might also be responsible for the development of cancers at both sites.[27, 28)] The present findings are most likely to be explained by the changes in the prevalence of these risk factors. In addition, there is a possibility that changes in diagnostic procedures and the introduction of cancer screening programs might influence time trends in cancer incidence. We obtained data on the prevalence of various known risk factors and other factors in Japan or in Miyagi Prefecture from published reports and compared them with the present results. The data are shown in Table IV. The prevalence data before World War II are not presented, because of incomplete data.

Based on the previous epidemiological studies, decreasing age at menarche,[29)] increasing age at first marriage[30)] and age at first birth,[31)] decreasing fertility rate[32)] and increasing adult height[33)] are likely to be related to the cohort effect on breast cancer incidence. But the increase in incidence at young age was merely observed in recent birth cohorts (Fig. 3) and the relative risks by birth cohort were irregular (Table II). Taking this result into consideration, it seems that recent changes in reproductive behaviors might not yet have produced a clear cohort effect. It may still take some time before the cohort effect emerges.

The significant period effect on breast cancer incidence in the present study might be related to increased diagnostic activities. Mammography was introduced in the

1960s and spread gradually,[34] and the breast cancer screening program started in 1977, in Miyagi Prefecture. However, the participation rate in screening being relatively low,[35] the impact of screening during the study period is likely to have been small. In the light of other various possible risk factors listed in Table IV, it seems that the most important factor producing the period effect may be changes in dietary habits, although the relationship between breast cancer and dietary habits is controversial.[27, 36] In Japan, the westernization of dietary habits has progressed since the end of World War II. Especially, intakes of energy, protein and fat per capita have increased rapidly.[37] The changes in these dietary intakes might be related to the period effect. In addition, it is possible that dietary habits may influence growth at an early age and endocrine events in life,[38] and promote the cohort effect in the future.

On the other hand, the role of exogenous hormones in the development of breast cancer has been noted and discussed in trend studies in Nordic countries.[10, 11] In Miyagi Prefecture, the recent usage rate of exogenous hormones is estimated to be 13.4%,[39] much lower than that in Nordic countries. The effects of exogenous hormones on breast cancer incidence seem likely to be trivial in Japan.

For cervical cancer, the direction of the association with reproductive factors is known to be opposite to that for breast cancer, and the trend of age-standardized incidence rate is quite inverse to that of breast cancer. Furthermore, our analyses indicate a declining trend in cervical cancer risk with successive time period, which was in contrast with the increasing trend in breast cancer risk. Although the cohort effect on cervical cancer incidence was marginal, the relative risks by birth cohort suggested a declining trend in younger birth cohorts. As this trend of cervical cancer risk with birth cohort is regarded as parallel with the changes of reproductive behavior, the cohort effect on cervical cancer incidence might be attributed to this factor. However, the difference in the patterns of birth cohort effects between breast and cervical cancers suggests that the roles of factors associated with cohort effects, including reproductive behavior, are very complex. The identification of unknown risk factors would also be needed.

The period effect on cervical cancer incidence is likely to be closely related to improvements of diagnostic procedure and the spread of screening programs.[40] According to a report on cancer screening, the number of cases of carcinoma *in situ* and dysplasia detected at screening was larger than that of invasive cancer registered.[35] As the detection and treatment of carcinoma *in situ* and dysplasia prevent the development of invasive cervical cancer, it seems that a decrease of risk with time period has been produced. Furthermore, in this study, the analyses on cervical cancer incidence were performed based on the corrected cervical cancer incidence. Although similar analyses were carried out for the official cervical cancer incidence and the results were consistent with those on the corrected values (data not shown), the cohort effect on the official cervical cancer incidence was statistically significant. As the small difference between official and corrected cervical cancer incidence is regarded as reflecting the trend of part-unspecified uterine cancer incidence, our results are likely to be slightly influenced by period effects relating to the reliability of incidence data during the study periods.

In conclusion, this study showed significant period effects on breast and cervical cancer incidences. The analyses of birth cohort effects revealed that the association of breast cancer risk with birth cohort was insignificant and irregular and that cervical cancer risk was declining in younger birth cohorts. Using published reports, the trnds in the prevalence of various risk factors were investigated. It was suggested that these effects might be related to the changes in prevalence of these risk factors and improvements of diagnostic procedure. But, the relations to several factors are still not clear. Successive observations are needed to elucidate the determinants of the trends in incidence.

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