

Fertility and Smoking: Mortality Due to Endometrial Cancer in Japan

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ABSTRACT

BACKGROUND: In Japan, the crude mortality rate (mortality rate) due to endometrial cancer is increasing. Using published data, the contributions of fertility and smoking, which are risk factors for endometrial cancer, were analyzed from the viewpoint of age and time.

MATERIALS AND METHODS: The data on the numbers of deaths due to endometrial cancer (ICD10 code, C54; from 1995 to 2019), live births, and female population were obtained from the website of Ministry of Health, Labour and Welfare of the Japanese Government (the vital statistics of Japan). The data on the smoking rates of females were obtained from the website of JT (Japan Tobacco). Pearson's correlation coefficients were calculated.

RESULTS: There was a large difference in the mortality rates of endometrial cancer between the groups aged 49 years or younger and the groups aged 50 years or older. There were strong negative

correlations between the birth rate in the group aged 20-29 years and the mortality rates in the groups aged 40-49 ($r=-0.901$) and 50-59 years ($r=-0.794$). However, there was no correlation between the birth rate in the group aged 20-29 years and the mortality rate in the group aged 60-69 years ($r=0.00$). There was a strong positive correlation between the birth rate in the group aged 30-39 years and the mortality rate in the group aged 50-59 years, which seems to reflect the delay in childbirth from the 20s to the 30s. There were positive correlations between the smoking rate in the group aged 20-29 and the mortality rates in the groups aged 40-49, 50-59 and 60-69 years ($r=0.882, 0.818, 0.896$, respectively). In contrast, there were negative correlations between the smoking rate in the group aged 50-59 years and the mortality rates in the groups aged 70-79 ($r=-0.702$) and 80-89 years ($r=-0.937$).

CONCLUSIONS: The preventive effects of giving birth in the 20s may be much larger than those of giving birth in the 30s. The contributions of smoking might vary, depending on the age at onset of this cancer and/or the duration of smoking. It is thus necessary to reexamine the contributions of the risk factors more minutely from the viewpoint of age and the period of exposure.

Key words: Endometrial cancer; Fertility; Mortality; Smoking

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INTRODUCTION

In 1950 in Japan, the crude mortality rate (mortality rate) of uterine cancer (cervical and endometrial cancer) was the second highest after gastric cancer among women. The mortality rate of uterine cancer gradually declined and in 1990 it fell to about one-fifth of that of 1950. In recent years, however, its mortality rate has been on the rise again, especially due to the increase in the number of deaths due to endometrial cancer.

Risk factors for type 1 endometrial cancer and type 2 are largely different^[1]. The risk factors investigated in this paper are those for type 1. There are various risk factors for type 1 endometrial

cancer such as obesity, nulliparity, early age at menarche, estrogen replacement therapy, and smoking^[2-4]. Epidemiological data about the birth rates and the smoking rates are published, but few reports have analyzed in detail the contributions of these two factors from the viewpoints of age and time.

Pearson's correlation coefficients were calculated.

MATERIALS AND METHODS

In Japan, the ICD10 has been used since 1995, and the code for endometrial cancer is C54. In this paper, the data on the numbers of deaths due to endometrial cancer for 25 years (from 1995 to 2019) are employed.

The data for the numbers of deaths due to endometrial cancer, live births, and the female population were obtained from the vital statistics of Japan (URL: <https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00450011&tstat=000001028897>).

The data for the smoking rates in females were obtained from the website of Japan Tobacco Inc. (JT). <http://www.health-net.or.jp/tobacco/product/pd090000.html>

RESULTS

1. Changes in the mortality rates of endometrial cancer by age group

The mortality rate (per 1,000,000 female population) of this cancer is increasing in all the age groups. There is a large difference in mortality rates between the groups aged 49 years or younger and the groups aged 50 years or older (Table 1).

2. The birth rates and the mortality rates of endometrial cancer

After the Second World War, in Japan, the mean age at the first marriage has risen^[5]. In 1950, the mean age of females at the first marriage was 23.0 years, but in 1980 it was 25.2, and in 2019, 29.4. The total fertility rate is declining. In 1950 it was 3.65, but in 2019 it was 1.36.

The birth rate (per 1,000 female population) has been declining among women in their 20s, but that for those in their 30s has been increasing (Figure 1). In 1966, the number of live births dropped greatly, since many believed in a superstition that a woman born in the year of the Fire Horse (one of the zodiac signs in Chinese astrology), which fell on 1966, would oppress her husband.

Table 2 shows the correlation coefficients between the birth rates of women in their 20s-30s and the mortality rates of those in their 40s, 50s, 60s, and 70s. Here correlation coefficients were calculated, e.g., for the mortality rates of women 60-69 years of age in the year 2000 compared to the birth rates of those 30-39 years of age in the year 1970.

There were strong negative correlations between the birth rates in the group aged 20-29 years and the mortality rates in the groups aged 40-49 ($r=-0.901$) and 50-59 years ($r=-0.794$). However, there was no correlation between the birth rate in the group aged 20-29 years and the mortality rate in the group aged 60-69 years ($r=0.00$).

There was a strong positive correlation between the birth rates in the group aged 30-39 years and the mortality rates in the group aged 50-59 years ($r=0.956$). The correlations between the birth rates in the group aged 30-39 years and the mortality rates in the groups aged 60-69 years ($r=-0.128$) and 70-79 years ($r=-0.406$) were weak.

3. The smoking rates and the mortality rates of endometrial cancer

Figure 2 shows the smoking rates in females by age group. There

Table 1 Mortality rates of endometrial cancer (per 1,000,000 female population).

Year	Age (years)						
	20-29	30-39	40-49	50-59	60-69	70-79	80-89
1995	0.0	1.3	6.4	26.4	45.6	39.7	52.1
1996	0.3	1.6	7.0	27.3	45.3	42.5	40.1
1997	0.4	0.8	6.6	25.2	45.4	39.0	52.5
1998	0.0	1.6	6.9	23.1	49.5	46.1	47.8
1999	0.4	0.7	7.2	23.1	44.8	36.0	49.4
2000	0.6	2.6	7.3	28.8	41.8	50.7	49.5
2001	0.0	2.0	7.6	29.7	48.6	56.1	58.8
2002	0.4	1.7	7.2	29.0	47.5	54.7	63.8
2003	0.0	2.2	6.5	32.5	48.7	56.4	61.3
2004	0.9	2.2	8.4	34.6	48.0	56.8	65.4
2005	0.4	2.7	7.9	34.6	52.4	56.7	52.8
2006	0.1	2.7	9.3	35.0	48.0	54.5	64.5
2007	0.3	1.8	8.2	33.8	54.0	65.6	75.9
2008	0.4	1.9	8.2	36.1	53.6	67.9	77.9
2009	0.0	3.4	8.1	34.4	53.1	58.1	67.7
2010	0.5	2.6	10.1	35.2	56.7	65.6	81.8
2011	0.2	3.6	10.2	40.7	60.3	72.8	88.4
2012	0.5	3.2	11.2	38.6	62.5	73.7	91.2
2013	1.0	4.1	10.7	39.3	60.7	72.5	95.3
2014	0.3	3.4	14.1	45.2	65.3	70.2	94.9
2015	0.5	2.2	12.8	45.6	66.3	77.4	95.6
2016	0.7	3.8	11.2	45.3	69.4	79.0	102.4
2017	0.9	4.3	14.3	45.8	75.8	79.1	103.3
2018	0.7	3.3	13.0	46.2	72.7	84.1	111.7
2019	0.5	2.8	14.4	49.7	74.1	79.8	103.1

Table 2 Correlation coefficients between birth rates and mortality rates of endometrial cancer.

	Mortality rates of endometrial cancer (age, years)				
		40-49	50-59	60-69	70-79
Birth rates (age, years)	20-29	-0.901*	-0.794*	0.000	
	30-39		0.956*	-0.128	-0.406

*P < 0.05

Table 3 Correlation coefficients between female smoking rates and mortality rates of endometrial cancer.

	Mortality rates of endometrial cancer (age, years)					
		40-49	50-59	60-69	70-79	80-89
Smoking rates (age, years)	20-29	0.882*	0.818*	0.896*		
	30-39		0.774*	0.405*	0.135	
	40-49			0.107	-0.795*	-0.700*
	50-59				-0.702*	-0.937*

*P < 0.05

is time lag from the start of smoking to the onset of endometrial cancer and consequently to death from this cancer. Table 3 shows the correlation coefficients between the smoking rates of women in their 20s, 30s, 40s, and 50s and the mortality rates in each of the age groups (40s, 50s, 60s, 70s, and 80s), under the assumption that the time lag is 20, 30 or 40 years. Here correlation coefficients were calculated, e.g., comparing the mortality rates of those 60-69 years of age in the year 2000 to the smoking rates of the group 30-39 years of age in the year 1970, when the time lag was assumed to be 30 years.

(1) From the viewpoint of age at death

The correlation coefficients of the ages at death of 40-49 and 50-

59 years were strongly positive, being about 0.8 (0.882 for death in the 40s vs. the smoking rate in the 20s, 0.818 for death in the 50s vs. the smoking rate in the 20s and 0.774 for death in the 50s vs. the smoking rate in the 30s). In contrast, the correlation coefficients for those in their 70s and 80s (all of them postmenopausal) were strongly negative (-0.795 for death in the 70s vs. the smoking rate in the 40s, -0.700 for death in the 80s vs. the smoking rate in the 40s, -0.702 for the smoking rate in the 50s vs. death in the 70s and -0.937 for death in 80s vs. the smoking rate in the 50s), except for one (0.135 for death in the 70s vs. the smoking rate in the 30s).

(2) From the viewpoint of the smoking age

The correlation coefficients of the smoking age of 20-29 years were strongly positive, being more than 0.8 (0.882 for the smoking rate in the 20s vs. death in the 40s, 0.818 for the smoking rate in the 20s vs. death in the 50s and 0.896 for the smoking rate in the 20s vs. death in the 60s). In contrast, the correlation coefficients of the smoking age of 50-59 years were strongly negative (-0.702 for the smoking rate in the 50s vs. death in the 70s and -0.937 for the smoking rate in the 50s vs. death in the 80s).

DISCUSSION

The subjects of case-control studies or cohort studies are usually living persons. But the present study employed mortality, and it was impossible to consider the contributions of, e.g., breast feeding and medication, since no information of individual patients was available.

The present conclusions are dependent mainly on correlation coefficients, which is a limitation. However, the important thing is that they show quite opposite results when the times or ages are different.

In Japan the age at the first delivery is becoming older. In 1950, it was 24.4 years, but in 2010, it was 29.9⁹⁾. The birth rates for those aged 30-39 years had positive correlations with the mortality rates for those aged 50-59 years. This may be a reflection of not giving birth in the ages of 20-29 years. That is, delivery in the 20s may have strong suppressive effects for this cancer. This might be due to the excretion of a large amount of progesterone during pregnancy in the 20s. The present results show that the contributions of delivery in the 20s are strongest for the mortality of women in their 40s and 50s, whose disease onset may be from the latter half of the 30s to the first half of the 50s. When the onset age is 60 or older, they may become weaker.

The present results suggest that the effects of smoking are dependent on the age of onset and/or duration of the period of smoking.

(1) Age at onset

According to the meta-analysis by Zhou et al.⁶⁾, smoking has suppressive effects against postmenopausal endometrial cancer, but the effects are not apparent in premenopausal women. This is consistent with the present findings that smoking rates had negative correlations with the mortality rates in the 70s and 80s. However, the present study suggests that it has promotive effects on the mortality rates in the 40s and 50s.

(2) Duration of smoking

The effects of smoking might be different depending on its duration. Considering the present results, smoking in the 20s may be promotive for the cancer, but smoking in the 50s may be suppressive. Most smokers in their 50s did not start smoking at the age of 50 years, but had continued to smoke since their teens or 20s. In other words, smokers in their 50s have been smoking for a long time. On the other

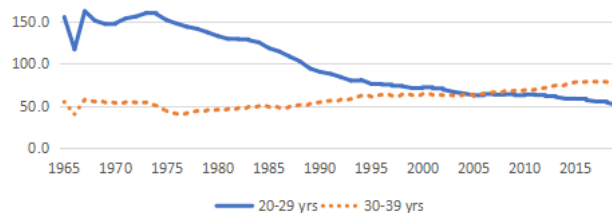


Figure 1 Birth rates (per 1,000 female population).

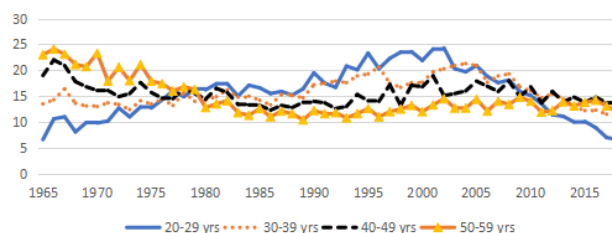


Figure 2 Female smoking rates (%).

hand, the smokers in their 20s in the present study were a mixture of those who will continue to smoke thereafter and those who will quit smoking, e.g., in their 30s, since many women quit smoking on the occasion of their marriage or pregnancy.

The present results indicating that smoking in the 20s is promotive for this cancer might mean that short-term smoking has harmful effects. In contrast, the suppressive results of smoking in the 50s might mean that long-term smoking has preventive effects. In other words, smoking for a relatively short period of time, e.g., 10-15 years or shorter may promote the cancer, but smoking over a long period of time, e.g., 30-35 years or longer may suppress this cancer and, as a result, the mortality rate of this cancer in postmenopausal women may decrease.

Thus, it is necessary to reexamine the contributions of fertility and smoking to endometrial cancer from the viewpoints of age and the period of exposure in more detail.

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