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BRIEF REPORT

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Burden of cancer attributable to exogenous hormone use in Japan in 2015

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Abstract: Exogenous female hormone use has not been as popular in Japan as in western populations. Here, we estimated the population-attributable fraction (PAF) of cancers in Japan in 2015 attributed to exogenous female hormone use. We used the most recent prevalence data for oral contraceptives (OC) and hormone replacement therapy (HRT), available from a large-scale population-based cohort study started in 2011-2016. For the purpose of this study, optimal usage of exogenous hormones was considered to be none. PAF was calculated for each age group using a standard formula. Overall, a negligible fraction, 0.4% of cancer incidence and 0.2% of cancer mortality in Japanese women was attributable to exogenous hormone use (OC use and HRT), and 0.2% of cancer incidence and 0.1% of cancer mortality overall when both sexes combined. The relatively low prevalence of exogenous hormone use in Japan compared to Western countries may explain the low fraction of cancer attributable to exogenous hormones among Japanese women.

***Keywords*:** cancer, exogenous hormone use, oral contraceptives, hormone replacement therapy, population attributable fraction, Japan

Introduction

In 2007, the International Agency for Research on Cancer (IARC) published a monograph on carcinogenic risk to humans that concluded that combined oral-progestogen contraceptives (OC) are carcinogenic to humans (*1*), particularly for cancers of the breast, cervix, and liver. On the contrary, however, there is also convincing evidence that these agents may act as protective factors for cancer of the endometrium and ovary.

The same review by IARC also concluded that, with regard to hormone replacement therapy (HRT), there is sufficient evidence in the association between combined estrogen-progestogen menopausal therapies and cancer of the breast (*1*). The finding of increased breast cancer risk associated with HRT has mainly been found among current users. Combined estrogen-progestogen menopausal therapy was considered to be carcinogenic to humans if progestogens are taken for less than 10 days per month; however, the risk for endometrial cancer was inversely associated with the number of days per month that progestogens are added to the regimens.

The usage of hormonal preparations in Japan has always been low. Despite the popularity of using HRT in the US and European nations, in 2011-2016, only 2.4% and 4.8% of women aged 40-74 had reported ever use of any type of OC and HRT, respectively, based on recent cohort study data in Japan (*2*).

In this report, we explore the population-attributable fractions (PAF) of cancers in Japan in 2015 attributed to exogenous female hormone use.

Materials and Methods

Cancers associated with exogenous hormone use

IARC has confirmed the usage of both OC (combined estrogen-progestogen) and HRT (combined estrogen-progestogen menopausal therapy) as Group 1, carcinogenic to humans (*3*). For the purpose of this study, we chose sites associated with OC and HRT for which IARC has found sufficient evidence for positive associations using available data on relative

risk. The cancer sites included in this report are breast, endometrium, and ovary.

Theoretical minimum risk exposure level

PAF of cancers associated with exogenous hormone use is the proportion of cancers diagnosed in a certain period in a population that could possibly have been prevented if no one in the population used OC or HRT. Accordingly, the optimal exposure to exogenous hormone use in this study was defined as no use. Analyses were conducted based on the type of exogenous hormone used (OC use or HRT).

Prevalence of exposure to hormonal use

No latent period was assumed in relation to female hormonal use, as current and recent users of female hormones are thought to be at the highest risk. To obtain Japanese data from a study or survey as close to 2015 as possible, we used data from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT) (*4*) for both OC and HRT use. These data were based on a self-administered questionnaire given at baseline, which included exogenous hormone use. The generally healthy women ($n \approx 60{,}000$) were asked if they had ever used OC and HRT. The baseline summary for OC and HRT use was reported (*2*). We further obtained age group-specific data from the research group for the purpose of this study. Since the JPHC-NEXT study includes participants aged 40-74, we assumed that the prevalence of OC use by those aged under 40 years was equal to that of those aged 40-44, and that the prevalence of HRT use by those aged over 75 was equal to that those aged 70-74.

Table 1 shows the proportion of the Japanese women with recent OC use and HRT by age group.

Cancer incidence and mortality in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*5*) using an age and period spline model, which are used as a short-term projection method for cancer incidence in Japan (*6*). The sex- and age-specific incidence data for target cancers were coded based on the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan (*7*). We obtained sex- and age-specific mortality data by cause of death from an available data source from the Health, Labour, and Welfare Statistics Association (*8*). Similarly to the cancer incidence data, 4-digit ICD-10 codes were used to classify the cause of death.

Estimates of relative risk of exposure to exogenous hormonal use

Given that previous studies on exogenous hormone use and cancer risk conducted in Japanese women were limited, we used results from global meta-analyses as described below.

OC use

Breast cancer: In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer (*9*) conducted an analysis of global epidemiological evidence on the association between use of OC and breast cancer risk. The relative risks associated with current and former use of OC (estrogen and progesterone) showed that OC use lead to a slight increase in risk.

Table 1. Proportion of exogenous hormone use with oral contraceptives (OC) and hormone replacement therapy (HRT) in Japan

Age at exposure and outcome (2015)	Proportion of oral contraceptive (OC) usage in the population (%)	Proportion of hormone replacement therapy (HRT) usage in the population (%)
10 - 14	0.0	0.0
15 - 19	0.0	0.0
20 - 24	3.5	0.0
25 - 29	3.5	0.0
30 - 34	3.5	0.0
35 - 39	3.5	0.0
40 - 44	3.5	1.3
45 - 49	2.8	3.4
50 - 54	2.4	6.3
55 - 59	0.0	6.5
60 - 64	0.0	5.9
65 - 69	0.0	5.9
70 - 74	0.0	4.8
75 - 79	0.0	4.8
80 - 84	0.0	4.8
≥ 85	0.0	4.8

Data source: Reference (*2,4*)

Table 2. Summary of risk estimates of site-specific cancers associated with exogenous hormone use for the present analysis

Factors	Cancer type	Studies	Reference group	Increase in risk
Oral contraceptive use	Breast	Collaborative Group on Hormonal Factors in Breast Cancer (1996) (*9*)	Never	1.07 ± 0.02*
	Endometrium	Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015) (*10*)	Never	0.69 (0.66 - 0.73)
HRT use	Ovary	Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008) (*11*)	Never	0.73 ± 0.02**
	Breast	Kim *et al.* (2018) (*18*)	Never	1.33 (1.24 - 1.44)
	Ovary	Meta-analysis of the result of prospective studies from Collaborative Group on Epidemiological Studies on ovarian Cancer (2015) (*19*)	Never	1.22 (1.06 - 1.38)

*Standard deviation. **Standard error.

Endometrial cancer: In 2007, IARC concluded that there is strong evidence that the use of estrogen-progestogen OC has a protective effect against carcinogenicity in the endometrium (*1*). Based on their review of four cohorts and 21 case-controls, risk for endometrial cancer among women who had taken these medications, and the reported risk reduction generally correlated with the duration of use and persisted for at least 15 years after cessation of use. A more recent meta-analysis published in 2015 (*10*) echoed these previous findings, although the risk reduction was marginally smaller.

Ovarian cancer: A 2007 review by IARC concluded that OC use had a protective effect against ovarian cancer among women (*1*). Not only was risk reduction associated with the duration of OC use, its protective effect persisted over two decades. An analysis conducted by the Collaborative Group on Epidemiological Studies of Ovarian Cancer in 2008 (*11*) showed that ever users of OC had 27% risk reduction compared to never users.

HRT

Breast cancer: The magnitude of the risk of HRT for risk of breast cancer has now been well established, mainly through studies conducted in the United States, Europe, and the UK (*12-16*). In the Million Women Study (*17*), compared to never users, the RR of current HRT users was 1.66 (95% Confidence Interval (CI): 1.58-1.75), while among past HRT users the risk did not differ from never users. For the present study, we derived HR for breast cancer from a meta-analysis conducted by Kim *et al.* (*18*) conducted in 2018, which reported the pooled HR of 23 prospective cohort studies and two randomized controlled trials to be 1.33 (95% CI: 1.24-1.44).

Ovarian cancer: The RRs of ovarian cancer by duration of HRT use in current and past users was obtained from a meta-analysis of individual participant dataset (*19*). We further conducted a meta-analysis of these RRs to obtain a summary RR of HRT use in ovarian cancer.

Table 2 shows a summary of the studies used in this estimate to derive RRs.

Estimation of population attributable fractions (PAFs)

PAF was calculated using the standard formula (*20*):

$$\mathrm{PAF} = \frac{P \times (RR - 1)}{P \times (RR - 1) + 1}$$

Where *P* refers to the prevalence of hormonal usage by age. For the PAF estimation, we included age 20-54 for OC use and age 40 and over for HRT use. The numbers of attributable cancers were then totalled across age categories to show a percentage of the total number of all incidence and mortality of cancer in Japan in 2015.

Results and Discussion

Table 1 shows the proportion of exogenous hormone use among Japanese women around 2015 by age group. Around 3% in the age 20-54 group was using OC and around 5% of the population aged 40 and over was using HRT.

Table 2 shows a summary of risk estimates for each of the cancer sites associated with exogeneous hormone use. For the present study, we included breast cancer for OC use and breast and ovarian cancer for HRT use.

The estimated PAF of cancer incidence and mortality in 2015 attributed to exogenous hormone use (OC use and HRT), individually and aggregated in Japan is summarized in Table 3. In the Japanese setting, only breast cancer incidence and mortality were attributable to OC use, with 62 incident cases and 5 deaths. Accordingly, the overall PAF for OC use was 0.02% for cancer incidence and 0.003% for cancer mortality in Japanese women. Likewise, breast and ovarian cancer were attributed to recent HRT, accounting for 1,391 cases and 274 deaths. Overall PAF for the HRT was 0.3% for cancer incidence and 0.2% for cancer mortality. In total, 0.4% of all cancer incidence and 0.2% of all cancer mortality in Japanese women in 2015 were attributable to exogenous hormone use, and 0.2% of total cancer incidence and 0.1% of total cancer

Table 3. Proportion (%) of cancer in 2015 attributable to exogenous hormone use in Japan

Factors	Incidence		Mortality	
	Women	Both sexes	Women	Both sexes
Oral contraceptive use (OC)				
Breast (C50)	0.1		0.04	
Endometrium (C54)	0.0		0.0	
Ovary (C56)	0.0		0.0	
Total cancer (C00-C96)	0.02		0.003	
Hormone replacement therapy (HRT)				
Breast (C50)	1.5		1.6	
Ovary (C56)	1.0		1.1	
Total cancer (C00-C96)	0.3		0.2	
Exogenous hormone use (OC and HRT)				
Breast (C50)	1.6	1.2	1.6	1.6
Endometrium (C54)	0.0	0.0	0.0	0.0
Ovary (C56)	1.0	1.0	1.1	1.1
Total cancer (C00-C96)	0.4	0.2	0.2	0.1

mortality when both sexes were combined. Detailed results for each cancer, sex, and age group are shown for in Tables S1-S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=37*).

In this study, we estimated the impact of exogenous hormone use on cancer incidence and mortality among Japanese women in 2015. We found that 0.4% of all cancer incidence and 0.2% of all cancer mortality were attributable to exogenous hormone use by Japanese women. Our findings (0.02% for OC, 0.3% for HRT among Japanese women) are lower than those from recent studies in Australia for 2010 (*21-23*) and in the UK for 2015 (*24*), where PAFs among overall cancers in women in Australia were 0.3% for OC use and 1.1% for HRT use, and 0.5% and 0.8% in the UK, respectively. The low prevalence data for OC and HRT use in Japan applied in this study may explain the low PAF of cancer attributable to exogenous hormones. Published data on the prevalence of exogenous hormone use in Japanese are limited. In the present study we used the most recent prevalence data for OC and HRT usage from the baseline data of a large-scale cohort study obtained in 2011-2016, which reflect recent exposure level to exogenous hormone use in the general Japanese population. The Japan Nurses' Health Study (JNHS) reported the prevalence of OC and HRT use among female nurses by cross-sectional survey between 2001-2007 (*25*), in which the lifetime prevalence of exogenous hormone use was 6.0% for OCs and 13.8% for HRT, albeit that these are relatively high compared with other studies focusing on general Japanese populations (*2,26*). According to the recent estimates from the United Nations that showed the estimated prevalence of contraceptive use among women of reproductive age (15-49) in 2019, the estimated prevalence of use of the pill was 2.9% in Japan (*27*), which accorded with our referenced data. We applied the prevalence data closest to the year 2015, and in the general population. More accurate estimates for risk would allow a better understanding of the impact of usage of exogenous hormones on cancer burden among Japanese women.

Conclusion

Our estimate found an overall negligible fraction, 0.4% of cancer incidence and 0.2% for cancer mortality in Japanese women, was due to exogenous hormone use (OC use and HRT). The low fraction of cancer attributable to exogenous hormones among Japanese women may be explained by the relatively low prevalence of exogenous hormone use in Japan compared with Western countries.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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