

Burden of cancer attributable to never breastfeeding in Japan in 2015

Mayo Hirabayashi¹, Chisato Nagata², Sarah Krull Abe¹, Eiko Saito³, Megumi Hori³, Kota Katanoda³, Tomohiro Matsuda⁴, Manami Inoue^{1,*}; the Cancer PAF Japan Collaborators

¹Division of Prevention, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan;

²Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan;

³Division of Cancer Statistics Integration, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan;

⁴National Cancer Registry Section Center for Cancer Registries Center for Cancer Control and Information Services/Office of International Affairs, Strategic Planning Bureau National Cancer Center, Japan, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan.

Abstract: We estimated the population attributable fraction (PAF) of cancers in Japan attributed to never breastfeeding in 2015. The data on breastfeeding in Japan were derived from two sources. Data on women aged younger than 40 were obtained from the Longitudinal Survey of Babies in the 21st Century (LSB21); those for women aged 40 to 69 was derived from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT). For the present study, the optimal frequency of breastfeeding was a history of ever breastfeeding. The PAF was calculated for each age group using a standard formula. Overall, 0.3% of total cancer incidence and 0.1% of total cancer mortality in Japanese women were attributable to never breastfeeding. The high prevalence of women who breastfed children may explain the lower fraction of cancer attributable among Japanese women compared to studies from other parts of the world.

Keywords: cancer, breastfeeding, population attributable fraction, Japan

Introduction

The Continuous Update Report (CUP) on Food, Nutrition, Physical Activity and Prevention of Cancer by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that there is probable evidence for an association between breastfeeding and decreased risk of breast cancer (1). In 2002, the Collaborative Group on Hormonal Factors in Breast Cancer showed that for every year of breastfeeding, the risk of breast cancer decreases by 4.3% (2). On the other hand, the association between breastfeeding and cancer risk of female reproductive organs is unknown. There is a limited or suggestive evidence for an association between breastfeeding and increased risk for ovarian cancer (1). While that report also discussed evidence for endometrial cancer, it was considered too limited to allow the drawing of a conclusion (1).

Here, we estimated the population-attributable fractions (PAF) of cancer incidence and mortality in Japan in 2015 attributed to never breastfeeding.

Materials and Methods

Cancers associated with breastfeeding

We defined the PAF of cancers associated with breastfeeding as the proportion of cancers diagnosed in a certain period in a population that could possibly have been prevented if everyone in the population ever breastfed children. In this study, we included cancers that were discussed in the WCRF/AICR CUP project (1). The cancer sites included in this estimate were breast, endometrium, and ovary.

Theoretical minimum risk exposure level

The optimum level of breastfeeding was considered as a history of ever breastfeeding.

Prevalence of breastfeeding

The latent period between cancer onset and breastfeeding is unknown. Therefore, for this study, we decided the optimal exposure to breastfeeding is a history of ever breastfeeding. Since 2001, the Japanese Ministry of Health, Labour and Welfare (MHLW) has been implementing a survey, called the Longitudinal Survey of Babies in the 21st Century (LSB21), with the aim of developing strategies to combat the declining fertility rate in Japan (3). The LSB21 surveyed families from all over Japan with newborns delivered between the

10th and 17th of January or July of 2001. The baseline questionnaire was sent to all of the families six or seven months after the baby was born. Follow-up questionnaires were then sent annually. Each participating child's birth records were linked with the Japanese vital statistics, which includes information such as birth length and weight, gestational age, sex and parental age.

For the history of breastfeeding, LSB21 obtained this information from the baseline questionnaire. The question asked whether the mother breast fed, formula fed, or both, in addition to the duration (ranging from zero to seven months). For people aged 40 and over, we used data from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT), launched in 2011 (4). JPHC-NEXT is population-based cohort study being conducted in seven prefectural areas all over Japan. Self-administered questionnaires about lifestyle were provided to all residents aged 40 to 74 at the time of the baseline survey. The questionnaire asked female participants if they had ever breastfed their child, and if they answered yes, the duration. Table 1 shows the proportion of women who were breastfeeding in 2005.

Cancer incidence and mortality in 2015

Cancer incidence in 2015 was estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (5). Estimation was done using an age and period spline model, a type of analysis which is used for short-term projection of cancer incidence in Japan (6). The sex- and age-specific incidence data for target cancers were coded in accordance with 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 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). Similar to the cancer incidence data, 4-digit ICD-10 codes we used to classify the cause of death.

Estimates of relative risk of history of breastfeeding

Table 2 shows a summary of relative risk estimates used in the present estimate, in which relative risk (RR) was measured compared to women who had no history of breastfeeding. The estimates, derived from the studies listed, were adjusted for potential major confounders. For breast (9) and ovarian cancer (10), the RRs were derived from a Japanese-based cohort study among women who were parous. For the risk of endometrial cancer, the RR was derived from a meta-analysis consisting of 15 studies, including three Japanese studies (11).

Since RRs for ever breastfeeding compared with never were estimated for the target cancers, we calculated the reciprocal of each RR to obtain the RR for never breastfeeding versus ever.

Estimation of population attributable fractions (PAFs)

PAF was calculated using the standard formula (12):

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

Where P refers to the prevalence of never breastfeeding by age. The numbers of attributable cancers were then totalled across age categories, in order to show a percentage of the total number of all cancer incidence and mortality in Japan in 2015.

Table 1. Staining Intensity of ALM and SSM lesions

Age at exposure (2005)	Proportion of ever breastfeeding (%)	
	Ever (%)	Never (%)
0 - 4	0	100
5 - 9	0	100
10 - 14	0	100
15 - 19	0	100
20 - 24	94	6
25 - 29	94	6
30 - 34	94	6
35 - 39	94	6
40 - 44	94.4	5.6
45 - 49	93.5	6.5
50 - 54	91.2	8.8
55 - 59	90.4	9.6
60 - 64	90.6	9.4
65 - 69	92.1	7.9
70 - 74	92.1	7.9
≥ 75	92.1	7.9

Results and Discussion

Table 1 shows the proportion of Japanese women with ever and never experience of breastfeeding in 2005 by age group. Among women aged 20 and over, over 90% have breastfed at least once. In comparison to women who had no history of breastfeeding women who breastfed had the following RR: breast 0.86 (0.65-1.15) (9), ovarian 1.00 (0.5-1.90) (10), and 0.88 (0.72-1.06) (11) (Table 2).

The estimated PAF of cancer incidence and mortality in 2015 attributed to never breastfeeding in Japan is summarized in Table 3. 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=38>). In the Japanese setting, the only breast

Table 2. Summary of risk estimate of site-specific cancers associated with breastfeeding for the present analysis

Factors	Cancer type	Studies	Reference group	Decrease in risk
Breastfeeding	Breast	Iwasaki <i>et al.</i> (2007) (9)	Never	0.86 (0.65 - 1.15)
	Ovarian	Weiderpass <i>et al.</i> (2012) (10)	Never	1.00 (0.5 - 1.90)
	Endometrium	Zhan <i>et al.</i> (2015) (11)	Never	0.88 (0.72 - 1.06)

Table 3. Proportion (%) of cancer in 2015 attributable to never breastfeeding in Japan

Factors	Incidence		Mortality	
	Women	Both sexes	Women	Both sexes
Breast (C50)	1.3		1.3	
Endometrium (C54)	1.1		1.1	
Ovary (C56)	0.0		0.0	
Total cancer (C00-C96)	0.3	0.1	0.1	0.1

cancer incidence and mortalities attributable to never breastfeeding were of breast and endometrium, with about 1% of incidence and mortality for each (breast: 1,066 attributable cases, 176 attributable deaths; endometrium: 165 attributable cases, 22 attributable deaths). Overall, in 2015, there were 1,231 cases and 202 deaths attributable to a history of never breastfeeding in 2005. Accordingly, the overall PAF for never breastfeeding was 0.3% for cancer incidence and 0.1% for cancer mortality in Japanese women.

In this report, we used RRs calculated for cancers in relation to never breastfeeding on the number of cancer incidence and mortality among Japanese women in 2015. We estimated that 1,231 cancer incident cases (0.30% of total cancer incidence) and 202 cancer deaths (0.13% of total cancer mortality) in 2015 could be attributed to never breastfeeding. These estimates are relatively low compared to results from the United Kingdom (UK) (1.5%) (13) but similar to the results from Australia (0.5%) (14).

With regard to breast cancer risk, these UK and Australian studies (13,14) found that 4.7% and 1.7% of cases were attributable to breastfeeding, respectively. These numbers are higher than our present finding (1.3%). This could be attributable to the difference in the proportion of women who have breastfed, as well as in the duration of breastfeeding used for calculation. In the UK (13) and Australia (14), 52-66% and 83% of women had initiated breastfeeding upon the birth of a child in 2000 and 2001, respectively. Compared to these two Western studies, over 90% of all Japanese women included in the study had breastfed. Further, the definition used as a history of breastfeeding differed - while the UK and Australia studies had clear definitions of what was considered breastfeeding, our study defined a history of breastfeeding as a history of ever breastfeeding. The result from Australian study suggested that breastfeeding for less than 12 months is associated with an increased risk of cancer. Given these methodological differences,

it is difficult to make direct comparisons between these previous and our present studies.

The protective effect of breastfeeding on breast cancer is not direct, but likely an indirect cause, such as due to lactation. According to the CUP project, the reduction in breast cancer may result from the hormonal influence of the associated period of amenorrhea and infertility (1). A longer lactation period leads to a reduced number of menstrual cycles throughout life, altering the cumulative exposure to sex hormones, which are known risk factor for post-menopausal breast cancer. The exfoliation of breast tissues during lactation, as well as the apoptosis of epithelial cells after the breastfeeding period is over, might eliminate cells with DNA damage and mutations, leading to lower breast cancer risk (1).

A more accurate history of lactation history estimates for risk would allow a better understanding of the impact of possible protective factors of breastfeeding on cancer burden among Japanese women.

Conclusion

Our estimate found an overall 0.3% of total cancer incidence and 0.1% of total cancer mortality in Japanese women was attributable to never breastfeeding. The high prevalence of women who breastfed may explain the lower fraction of cancer attributable among Japanese women compared to studies from other parts of the world.

Funding: This study was supported by JSPS KAKENHI Grant Number 16H05244.

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

References

1. World Cancer Research Fund/American Institute for

- Cancer Research. Diet, Nutrition, Physical activity and Cancer: a global perspective. The Third Expert Report. 2018. <https://www.wcrf.org/wp-content/uploads/2021/02/Summary-of-Third-Expert-Report-2018.pdf> (accessed November 1, 2021).
2. Lambe M, Hsieh CC, Chan HW, Ekblom A, Trichopoulos D, Adami HO. Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden. *Breast Cancer Res Treat.* 1996; 38:305-311.
 3. Ministry of Health Labour and Welfare. Outline of the first longitudinal survey of babies in 21st Century. <http://www.mhlw.go.jp/english/database/db-hw/babies02/index.html> (accessed November 1, 2021).
 4. Sawada N, Iwasaki M, Yamaji T, *et al.* The Japan public health center-based prospective study for the next generation (JPHC-NEXT): study design and participants. *J Epidemiol.* 2020; 30:46-54.
 5. Cancer Statistics. Cancer Information Service, National Cancer Center, Japan (Monitoring of cancer incidence in Japan (MCIJ)) https://ganjoho.jp/reg_stat/statistics/data/dl/en.html (accessed October 20, 2021).
 6. Katanoda K, Kamo K, Saika K, Matsuda T, Shibata A, Matsuda A, Nishino Y, Hattori M, Soda M, Ioka A, Sobue T, Nishimoto H. Short-term projection of cancer incidence in Japan using an age-period interaction model with spline smoothing. *Jpn J Clin Oncol.* 2014; 44:36-41.
 7. Cancer Statistics. Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan, Ministry of Health, Labour and Welfare) https://ganjoho.jp/reg_stat/statistics/data/dl/en.html (accessed November 8, 2021).
 8. Ministry of Health Labour and Welfare. Sex and age specific mortality statistics in Japan (2015) by ICD-10, by 4-digit. Health, Labour and Welfare Statistics Association. <http://www.hws-kyokai.or.jp/information/mortality.html> (accessed October 20, 2021). (in Japanese)
 9. Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S; Japan Public Health Center-based Prospective Study Group. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. *Eur J Cancer Prev.* 2007; 16:116-123.
 10. Weiderpass E, Sandin S, Inoue M, Shimazu T, Iwasaki M, Sasazuki S, Sawada N, Yamaji T, Tsugane S. Risk factors for epithelial ovarian cancer in Japan - results from the Japan public health center-based prospective study cohort. *Int J Oncol.* 2012; 40:21-30.
 11. Zhan B, Liu X, Li F, Zhang D. Breastfeeding and the incidence of endometrial cancer: A meta-analysis. *Oncotarget.* 2015; 6:38398-38409.
 12. LEVIN ML. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum.* 1953; 9:531-541.
 13. Brown KF, Rungay H, Dunlop C, Ryan M, Quartly F, Cox A, Deas A, Elliss-Brookes L, Gavin A, Hounsoms L, Huws D, Ormiston-Smith N, Shelton J, White C, Parkin DM. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer.* 2018; 118:1130-1141.
 14. Jordan SJ, Wilson LF, Nagle CM, Green AC, Olsen CM, Bain CJ, Pandeya N, Whiteman DC, Webb PM. Cancers in Australia in 2010 attributable to total breastfeeding durations of 12 months or less by parous women. *Aust N Z J Public Health.* 2015; 39:418-421.
- Received June 12, 2021; Revised November 17, 2021;
Accepted December 8, 2021.
- Released online in J-STAGE as advance publication December 13, 2021.
- *Address correspondence to:*
Manami Inoue, Division of Prevention, Center for Public Health Sciences, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan.
E-mail: mnminoue@ncc.go.jp