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Original Article

Estimation of Population Attributable Fraction by Hormone and Reproductive Factors on Female Cancer in the Republic of Korea, 2015 to 2030

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Purpose Population attributable fractions (PAFs) for hormone and reproductive factors have been estimated in several countries. International Agency for Research on Cancer (IARC) designated as group 1 and group 2A carcinogen for hormone factors in breast, ovarian, endometrial and uterine cervix cancer. This study aimed to estimate the PAFs of hormone/reproductive factor attributed to cancer incidence and deaths in Korean women and projected trends from 2015 to 2030.

Materials and Methods The PAF was estimated with using the 2005 standardized prevalence rates and 2020 incidence and deaths with a 15-year latency. Based on the Levin's formula, prevalence rates were calculated using the Korea National Health and Nutrition Examination Survey (KNHANES) and the relative risks, which were the risk of selected female cancer associated with oral contraceptive, hormone replacement therapy and duration of breastfeeding, were estimated from the meta-analysis of studies performed in Korean women population. Studies based on the Asian and Global populations were calculated as a sensitivity analysis.

Results The estimation PAFs for hormone was 1.02% with 1,192 cases and reproductive was 2.67% with 3,112 cases. Moreover, 0.40% (125 deaths) and 1.09% (342 deaths) in female-related cancer deaths in order. Estrogen-progesterone combined hormone replacement therapy (HRT) accounted the most proportion in hormone factors and breastfeeding in reproductive factors. Also, the breast cancer had the highest percent in both hormone and reproductive factors.

Conclusion Through this study, 1.02% and 2.67% of female-related cancer incidence will be reduced by encouraging avoiding the use of oral contraceptives and HRT and breastfeeding for more than 6 months in reproductive factors. Additionally, among four selected female cancers in this study, breast cancer was observed to be a significant level of prevention.

Key words Hormone and reproductive factors, Population attributable fraction, Breast neoplasms, Trend change

Introduction

The International Agency for Research on Cancer (IARC) under the World Health Organization designated group 1 and group 2A as hormonal factors for female cancers such as breast, ovarian, endometrial, and cervical uterine cancers. In the case of breast cancer, estrogen-progesterone (EP) oral contraceptives (OC) and EP menopausal therapy were designated as group 1 factors, and estrogen-menopausal therapy was designated as group 2A. EP OC were categorized as group 1 for uterine cervical cancer. Estrogen-only therapy and EP menopausal therapy in postmenopausal women were classified as group 1 for endometrial cancer. Finally, for ovarian cancer, estrogen therapy in postmenopausal women is classified as a group 1 factor [1,2].

In addition, the evidence of breastfeeding, which is one of reproductive factors, is suggested by a report published in 2011 by the World Cancer Research Fund International (WCRF), which is an international organization that estimates the results of cancer risk and prevention. It suggested that there is 'convincing' evidence that none-experience of breastfeeding increase the risk of breast cancer in premenopausal women and also in postmenopausal women [3].

The contribution of cancers due to external hormones and reproductive factors based on the Korean population was estimated by the National Cancer Center in 2009 using the 1990 exposure rates of hormone/reproductive and incidence cases and deaths in 2009 [4,5]. Since it has been 15 years ago from now, the estimation of population attributable fraction (PAF) needs to be updated. Also, it was estimated based on a case-control study and included only breast and ovarian cancers. Moreover, the use of OC and hormone replacement therapy (HRT) among Korean women is increasing compared to the past. Among Korean women, the rise of

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women's status and increasement of participating in the workforce have naturally led to decline the births rate and breastfeeding [6,7].

In this study, OC and HRT as hormonal factors and breastfeeding as reproductive factors were finally selected in accordance with existing previous reports or studies and the reality of Korean women. Therefore, we aimed to estimate the population attributable factors of hormones and reproductive factors to women-related cancer incidence and deaths in 2015, considering the exposure rates in 2000. Furthermore, this study will estimate the trends in hormonal and reproductive factors (2020, 2025, and 2030) compared to the past.

Materials and Methods

1. Definition of exposure

The theoretical minimal risk of exogenous hormones has not been reported. In Korea, only EP combination pills are sold as OC pills, whereas estrogen, progesterone, EP combinations, and tibolone are prescribed for menopausal HRT. Diethylstilbestrol was excluded because it has not been officially prescribed under insurance coverage for Korean women [8].

The WCRF/American Institute for Cancer Research has provided strong evidence with a probable causality that breastfeeding may reduce the risk of breast cancer [9]. The protective effect of breastfeeding on ovarian cancer is suggested but currently has limited evidence, and its effect on uterine cancer has not been evaluated. Based on the fact that breastfeeding for more than 6 months lowers the risks of breast cancer [10], previously published PAF studies also adopted these standards [11], the median breastfeeding among Korean women was 5 months [12], and lastly, the Korean National Health and Nutrition Examination Survey (KNHANES), which was used to estimate the prevalence of breastfeeding, also used 6 months as the standard, therefore, the study defined "breastfeeding more than 6 months" as theoretical minimum risk exposure distribution for cancer and defined "breastfeeding more than 6 months" as a risk factor (S1 Table).

2. Estimation of relative risks for cancer risk

Cancers related to OC pills were selected as breast (C50), uterine cervical (C53), endometrial (C54.1), and ovarian cancer (C56). HRT was subdivided into EP combined, progesterone, estrogen (E) only, and tibolone, and the related cancers were selected. Breast cancer (C50) was selected as a risk factor for breastfeeding.

The relative risks (RRs) of hormone/reproductive factors for cancer risk were calculated using a meta-analysis of individual RR derived from cohort studies. Individual RRs were obtained through a systematic review of Asian and global cohort studies and raw data analysis of seven Korean cohort studies by the Korean Cohort Consortium [13]. The studies included in the systematic review of Asian and global cohort met the following criteria: (1) studies that involved outcomes of hormone/reproductive factors and female cancer, (2) studies that offered RRs, odds ratios, hazard ratios, and (3) cohort studies based on Asian and global populations. If case-control studies had to be included owing to a lack of cohort studies, the following exclusion criteria were applied: (1) single center and (2) patients less than 500 individuals.

Those Korean cohort studies are as follows: the Korean National Health Insurance Service-National Health Screening Cohort (KNHIS) [14], the Korean Multi-center Cancer Cohort Study (KMCC) [15], the Namwon/Dong-gu Study (NWS/DGS) [16], the Korean Cancer Prevention Study II (KSCP II) [17], the Korean National Cancer Center Screening Cohort (KNCC) [18], Health Promotion through Early Detection and Control of Cancer cohort (H-PEACE) [19], and the Kangbuk Samsung Health Study (KSCS) [20].

Heterogeneity among studies was estimated using Higgins and Thompson's I^2 statistic and p-values in Cochran's Q statistics. Publication bias was evaluated using p-values from Egger and Begg tests. Statistical analysis was conducted using the R packages ver. 3.5.2 (https://www.r-project.org/) statistical software.

3. Prevalence of exposures to each risk factors

The prevalence of OC, postmenopausal HRT, and breastfeeding was estimated using KNHANES 2007-2020. Upon the data, the survey questions of each year regarding hormone were presented whether the participants were taking hormone ("Ever"). In case of breastfeeding, the categories were divided into non-childbearing, non-breastfeeding, less than 6 months, and more than 6 months of breastfeeding. Each year was age-standardized to the resident registration central population (RRCP) of 2000, and each of these values was extrapolated using optimal modeling (linear regression model) to calculate the prevalence rates in 2000. The prevalence rates of OC and postmenopausal HRT were calculated in age < 55 and age ≥ 50, respectively, and those of breastfeeding were calculated in all women aged ≥ 20, when performing age-standardization. The prevalence rates of HRT by type were calculated by multiplying the prevalence rates of HRT by the usage the proportion rate for each type, which was derived from the KNHIS data for, 2002-2013.

4. Analysis of the PAFs

The PAF (%) for hormonal and reproductive risk factors was calculated using the Levin formula, and 95% confidence

Table 1. PAF[a)] of cancer attributable to hormone and reproductive factors from 2015 to 2030

	Women								Total							
	2015		2020		2025		2030		2015		2020		2025		2030	
	PAF	AC	PAF	AC	PAF	AC	PAF	AC	PAF	AC	PAF	AC	PAF	AC	PAF	AC
Incidence																
By carcinogen																
OC	0.06	62	0.01	9	–0.01	–14	–0.06	–105	0.03	62	0.00	9	0.00	–14	–0.03	–105
HRT																
EP-combined	0.39	398	0.53	613	0.84	1,219	0.82	1,460	0.18	398	0.25	613	0.41	1,219	0.41	1,460
E-only	0.21	210	0.26	307	0.34	493	0.33	590	0.10	210	0.12	307	0.16	493	0.16	590
Progesterone	0.05	55	0.05	59	0.05	68	0.01	22	0.03	55	0.02	59	0.02	68	0.01	22
Tibolone	0.10	98	0.17	203	0.30	430	0.38	683	0.05	98	0.08	203	0.14	430	0.19	683
Breastfeeding	2.29	2,335	2.67	3,112	3.14	4,568	3.22	5,743	1.08	2,335	1.26	3,112	1.52	4,568	1.56	5,743
By cancer type																
Breast (C50)	3.01	3,060	3.63	4,238	4.55	6,624	4.71	8,408	1.42	3,060	1.72	4,238	2.21	6,624	2.34	8,408
Uterine (C53)	0.13	127	0.09	102	0.05	68	0.04	68	0.06	127	0.04	102	0.02	68	0.02	68
Ovarian (C56)	–0.03	–31	–0.03	–31	–0.01	–16	–0.06	–104	–0.01	–31	–0.01	–31	–0.01	–16	–0.03	–104
Endometrial (C54.1)	0.00	0	0.00	–5	0.06	87	0.01	20	0.00	0	0.00	–5	0.03	87	0.01	20
All cancer	3.10	3,157	3.69	4,303	4.65	6,764	4.70	8,392	1.46	3,157	1.75	4,303	2.25	6,764	2.34	8,392
Death																
By carcinogen																
OC	–0.05	–14	–0.10	–32	–0.10	–34	–0.24	–89	–0.02	–14	–0.04	–32	–0.04	–34	–0.09	–89
HRT																
EP-combined	0.21	60	0.25	79	0.38	131	0.36	132	0.08	60	0.10	79	0.15	131	0.14	132
E-only	0.13	37	0.15	46	0.19	64	0.20	73	0.05	37	0.06	46	0.07	64	0.08	73
Progesterone	0.03	10	0.03	9	0.03	9	0.01	3	0.01	10	0.01	9	0.01	9	0.00	3
Tibolone	0.05	13	0.07	23	0.12	43	0.17	61	0.02	13	0.03	23	0.05	43	0.07	61
Breastfeeding	0.97	283	1.09	342	1.28	437	1.31	479	0.37	283	0.42	342	0.49	437	0.51	479
By cancer type																
Breast (C50)	1.32	383	1.51	472	1.85	634	1.90	695	0.50	383	0.58	472	0.71	634	0.74	695
Uterine (C53)	0.07	19	0.05	15	0.03	11	0.03	12	0.02	19	0.02	15	0.01	11	0.01	12
Ovarian (C56)	–0.05	–16	–0.07	–23	–0.02	–7	–0.14	–50	–0.02	–16	–0.03	–23	–0.01	–7	–0.05	–50
Endometrial (C54.1)	0.01	2	0.01	3	0.03	12	0.01	3	0.00	2	0.00	3	0.01	12	0.00	3
All cancer	1.34	389	1.49	467	1.90	650	1.80	659	0.51	389	0.57	467	0.73	650	0.70	659

AC, number of attributable cancers; EP, estrogen-progesterone; HRT, hormone replacement therapy; OC, oral contraceptive; PAF, population attributable fraction. [a)]The PAF in the year was estimated by using the number of cancers among the population in the year under consistent relative risks and a 15-year latency period and the prevalence of hormone and reproductive factors in 2000, 2005, 2010, and 2015, respectively.

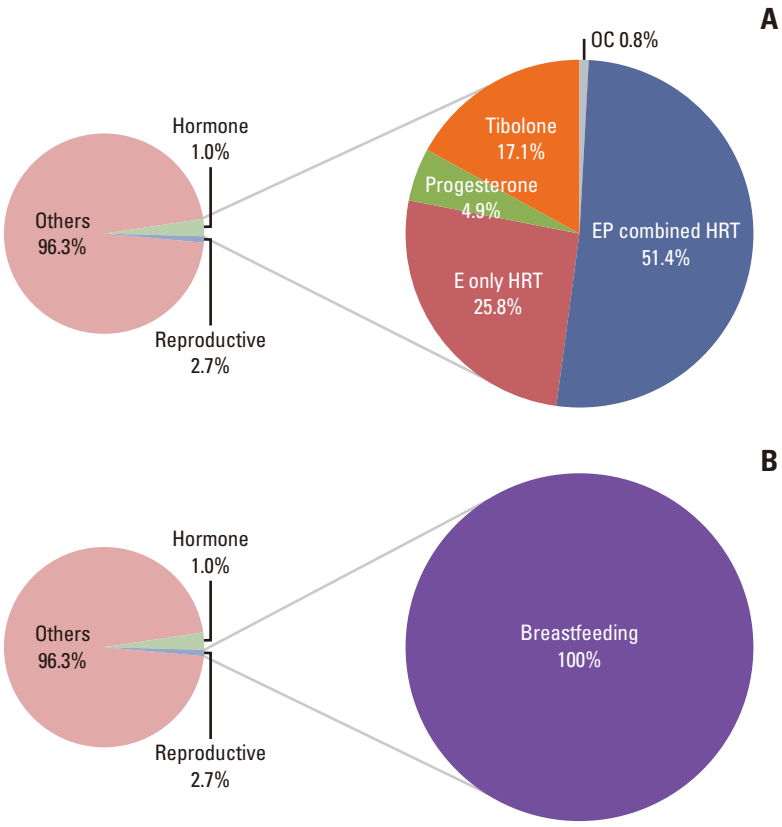

Fig. 1. Fraction (%) of cancer incidence caused by hormone and reproductive factors among women in Korea, 2020. (A) Hormone factors in women cancer cases, 2020. (B) Reproductive factor in women cancer cases, 2020. E, estrogen; EP, estrogen-progesterone; HRT, hormone replacement therapy; OC, oral contraceptive.

intervals (CIs) were estimated using the Monte Carlo method [21]. Considering the 15 latency periods, the PAF for cancer in 2015, 2020, 2025, and 2030 were estimated using the prevalence rates of 2000, 2005, 2010, and 2015 and consistent RR. Attributable cancer cases or deaths (attributable count; AC) were obtained from the 2015 Cancer Registration Statistics of the National Cancer Center for adults aged > 20 years. The number of cases and deaths due to OC were calculated for women under 50 years of age and 50-54 years old, while the number of cases due to postmenopausal HRT was calculated for women over 50 years of age. The AC of cancer cases and deaths due to breastfeeding were estimated in parous women. When estimating the risks of specific cancer deaths, the pooled RRs of specific cancer incidences were substituted. If RRs were less than 1, PAF and AC were calculated as negative values.

Results

1. Exposure rates

The prevalence rates of exposure to hormones and reproductive factors in 2000 are listed in S2 Table. The use of OC in 2000 was 8.91% in premenopausal women, and the use of HRT in 2000 was 11.44% in postmenopausal women. Considering the HRT type, the percentage of patients using combined EP-combined was 41.12%, E-only was 27.57%, tibolone was 18.5%, and progesterone was 12.84%. Applying each value with the exposure rate of ever-used HRT, the final prevalence rate of EP combined in 2000 was 4.70% (=11.44×0.4112), E-only 3.15%, tibolone 2.12%, and progesterone 1.47%.

Moreover, the duration of breastfeeding was 28.87% for no experience of breastfeeding with nulliparous women and 6.50% for breastfeeding for less than 6 months.

2. Relative risks of cancer

The RRs for breast, ovarian, endometrial, and cervical cancers applied in this study, along with the data sources, are summarized in S3 Table (S4-S17 Figs.).

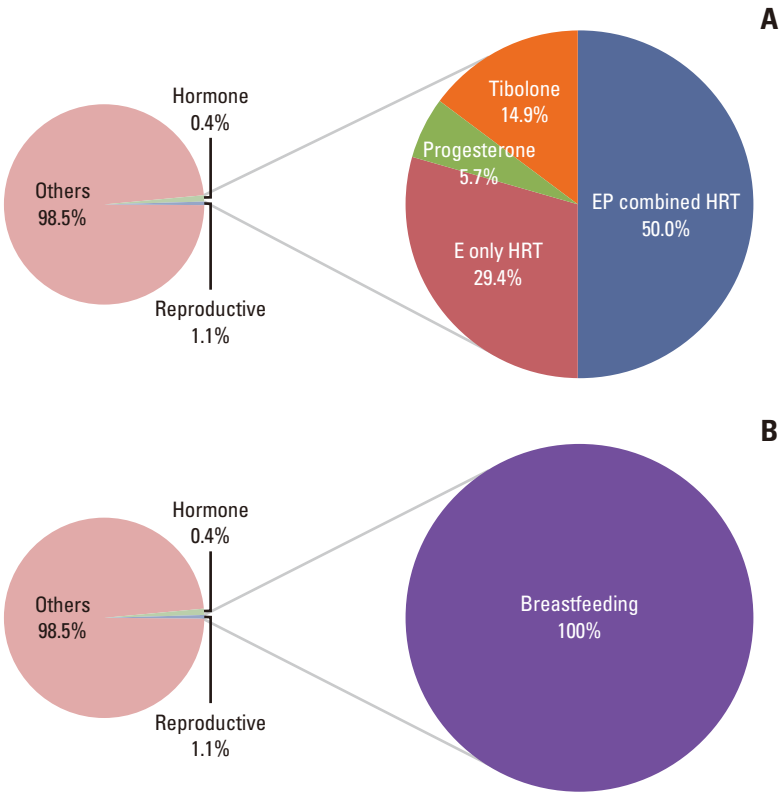

Fig. 2. Fraction (%) of cancer deaths caused by hormone and reproductive factors among women in Korea, 2020. (A) Hormone factors in women cancer deaths, 2020. (B) Reproductive factor in women cancer deaths, 2020. E, estrogen; EP, estrogen-progesterone; HRT, hormone replacement therapy.

Use of combined OC increased the breast and uterine cervix cancer risks (RR, 1.04; 95% CI, 0.80 to 1.35 and RR, 1.60; 95% CI, 1.23 to 2.09, respectively), whereas, decreased the ovarian and endometrial cancer risks (RR, 0.64; 95% CI, 0.43 to 0.95 and RR, 0.74; 95% CI, 0.69 to 0.80, respectively). Moreover, the use of HRT, including combined EP, E-only, progesterone, and tibolone, increased the risk of all four types of cancer.

Based on breastfeeding for more than 6 months, the risks of breast cancer increased by 53% (RR, 1.53; 95% CI, 0.98 to 2.42) and 37% (RR, 1.37; 95% CI, 1.04 to 1.82) when breastfeeding for less than 6 months or not breastfeeding at all.

The pooled RR of death for each cancer type was collectively replaced by the incidence of the RR to calculate each PAF.

3. PAF trend of cancer attributable to hormone and reproductive factors

The PAFs of cancers attributable to hormones and reproductive factors from 2015 to 2030 are shown in Table 1 (S18-S19 Table: for detailed information of 2015 PAF). Among the causes of female-related cancer in Korean women, the contribution of hormone/reproductive factors was 3.10% in 2015, with cancer incidence cases of 3,157, and 3.69% in 2020, cancer incidence cases of 4,303, 4.65% in 2025, cancer incidence cases of 6,764, and 4.70% in 2030, with cancer incidence cases of 8,392. The contribution rate increased by 1.60% over 15 years. Moreover, the PAF of cancer deaths was 1.34% in 2015, 1.49% in 2020, 1.90% in 2025, and 1.80% in 2030. Although the contribution rate of hormonal and reproductive factors decreased slightly between 2025 and 2030 (0.10% decrease), the projected value of PAF deaths has gradually increased since 2015.

Based on the PAF in 2020, the contribution of hormone factors was 1.02% (95% CI, 0.16 to 3.47) and reproductive factor was 2.67% (95% CI, 0.22 to 5.29). EP combined HRT had the highest contribution of 51.4% in the PAF of hormonal factors, and only breastfeeding contributed to the PAF of reproductive factors. In addition, the PAF for cancer deaths showed the same pattern as that for cancer incidence (Figs. 1 and 2).

Sensitivity analyses that calculated the PAF using Asian or global RRs are listed in Tables 2 and 3. The cancer incidence in PAF attributable to hormonal factors is estimated to be 0.86% in the Asian population and 0.54% in the global

Table 2. Sensitivity analysis: PAF (%) of cancer due to hormone factors in 2015 using Asian and global RR

Hormone factor	Incidence				Deaths			
	Women		Total		Women		Total	
	PAF using Asian RR (%)	PAF using global RR (%)	PAF using Asian RR (%)	PAF using global RR (%)	PAF using Asian RR (%)	PAF using global RR (%)	PAF using Asian RR (%)	PAF using global RR (%)
OC								
Breast (C50)	0.08	0.08	0.04	0.04	0.04	0.04	0.01	0.01
Uterine cervix (C53)	0.13	0.13	0.06	0.06	0.07	0.07	0.02	0.02
Ovarian (C56)	–0.04	–0.07	–0.02	–0.04	–0.06	–0.11	–0.02	–0.04
Endometrial (C54.1)	–0.05	–0.05	–0.03	–0.03	–0.02	–0.02	–0.01	–0.01
HRT								
EP-combined								
Breast (C50)	0.37	0.18	0.18	0.08	0.18	0.09	0.07	0.03
Ovarian (C56)	0.02	0.01	0.01	0.00	0.03	0.02	0.01	0.01
E-only								
Breast (C50)	0.14	0.06	0.07	0.03	0.07	0.03	0.03	0.01
Ovarian (C56)	0.02	0.02	0.01	0.01	0.03	0.03	0.01	0.01
Endometrial (C54.1)	0.04	0.04	0.02	0.02	0.02	0.02	0.01	0.01
Progesterone								
Breast (C50)	0.04	0.04	0.02	0.02	0.02	0.02	0.01	0.01
Ovarian (C56)	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.00
Endometrial (C54.1)	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Tibolone								
Breast (C50)	0.09	0.09	0.04	0.04	0.04	0.04	0.00	0.02
Ovarian (C56)	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00
By carcinogen								
OC	0.12	0.08	0.06	0.04	0.02	–0.04	0.01	–0.01
HRT								
EP-combined	0.39	0.19	0.18	0.09	0.21	0.10	0.08	0.04
E-only	0.21	0.12	0.10	0.06	0.13	0.08	0.05	0.03
Progesterone	0.05	0.05	0.03	0.02	0.03	0.03	0.01	0.01
Tibolone	0.10	0.10	0.05	0.05	0.05	0.05	0.02	0.02
By cancer type								
Breast (C50)	0.73	0.45	0.34	0.21	0.35	0.21	0.13	0.08
Uterine cervix (C53)	0.13	0.13	0.06	0.06	0.07	0.07	0.02	0.02
Ovarian (C56)	0.00	–0.04	0.00	–0.02	0.01	–0.03	0.00	–0.02
Endometrial (C54.1)	0.01	0.01	0.00	0.00	0.01	0.01	0.00	0.00
Hormone factors, all cancers	881	547	881	547	126	65	126	65
PAF	0.86	0.54	0.41	0.25	0.43	0.22	0.16	0.99

E, estrogen; EP, estrogen-progesterone; HRT, hormone replacement therapy; OC, oral contraceptive; PAF, population attributable fraction; RR, relative risk.

population. Moreover, cancer deaths due to PAF have been calculated to be 0.43% in the Asian population and 0.22% in the global population. The incidence and deaths of both PAFs due to reproductive factors are higher in Asians (incidence, 3.00%; deaths, 1.28%) than in the global population (incidence, 0.28%; deaths, 0.12%).

The comparison of PAF (%) in 2015 and in the past year (2009) reported by the National Cancer Center (NCC) are shown in S20 Table. According to the NCC, reproductive factors were calculated as hormonal factors, including OC and EP-combined HRT, at 0.78%, and reproductive factors, including parity and breastfeeding, at 2.34% for the risk of developing female-related cancers. This study suggested that 0.81% of hormonal factors included OC, EP-combined HRT, E-only HRT, progesterone, and tibolone, while 2.29% of reproductive factors included only breastfeeding.

Table 3. Sensitivity analysis: PAF (%) of cancer due to reproductive factor in 2015 using Asian and global RR

Reproductive factor	Incidence				Deaths			
	Women		Total		Women		Total	
	PAF using Asian RR (%)	PAF using global RR (%)	PAF using Asian RR (%)	PAF using global RR (%)	PAF using Asian RR (%)	PAF using global RR (%)	PAF using Asian RR (%)	PAF using global RR (%)
Breastfeeding								
Breast (C50)	3.00	0.28	1.42	0.13	1.28	0.12	0.42	0.04
By carcinogen								
Breastfeeding	3.00	0.28	1.42	0.13	1.28	0.12	0.42	0.04
By cancer type								
Breast (C50)	3.00	0.28	1.42	0.13	1.28	0.12	0.42	0.04
Reproductive factors, all cancers	3,059	280	3,059	280	371	34	371	34
PAF	3.00	0.28	1.42	0.13	1.28	0.12	0.42	0.04

PAF, population attributable fraction; RR, relative risk.

Discussion

This study aimed to estimate the contribution of hormone/reproductive factors to cancer in Korean women in 2020, compare the trend of PAFs over 5 years, and use various RRs. In 2020, the PAFs of cancer incidence caused by hormonal and reproductive factors were 1.02% and 2.67%, respectively. Hormone/reproductive factors are expected to increase by 1.60% from 2015 to 2030. When estimating PAF using various RRs, the contribution of hormonal factors was similar, with a value of less than 1%; however, the contribution of reproductive factors was the highest in the Asian population.

The PAFs for hormones and reproductive factors have been estimated in several countries. In Western countries, such as the UK, Australia, and Canada, external hormone uses and 6 months of breastfeeding were estimated as PAF in female cancer [22-24]. In the UK (2010), non-use of postmenopausal hormone therapy was the theoretical minimum risk exposure level for breast, endometrial, and ovarian cancers with 1.1% attributional fractions by using them, whereas breastfeeding for less than 6 months was considered a reference exposure, resulting in an attributable fraction of 1.7% [22]. In Australia (2010), attributable factors were calculated as 1.1%, 0.3%, and 0.5% for non-use of HRT in postmenopausal women with breast, endometrial, and ovarian cancer, non-use of combined OC in women with breast and cervical cancer, and breastfeeding for less than 12 months in women with breast cancer, respectively [23]. In Canada (2012), only hormonal factors including breast, endometrial, and ovarian cancers were considered and calculated as 1.7% for OC use and 0.9% for HRT use [24]. Moreover, in Asian countries, the current use of hormones was identified as a risk factor for all cancer cases, with a contribution of approximately 0.4% [25]. It is evident that the contribution of exogenous hormones to the total number of cancer cases is less than 4%, and the PAF of Western countries is higher than that of Asian countries (S21 Fig.).

This study is noteworthy due to the gradually increasing incidence of reproductive PAFs. Even though only the breastfeeding value was included, it increased from 2.29% in 2015 to 3.22% in 2030, with an increment of 0.93% being the only factor. This increase was due to the rapid increase in the prevalence of nulliparous women, which was 15.17% in 2015, 19.07% in 2020, 23% in 2025, and 25.97% in 2030. These phenomena reflect women's rising overall education and employment and the long period of settling into a proper position at work [26].

This study has several strengths. First, the pooled RRs based on the 2009 NCC report relied on the Seoul Breast Cancer Study (SeBCS) and Lee et al. [27], which were case-control studies. We calculated the risk of breast cancer using cohort studies conducted specifically in the Korean population. This study included four cohort studies on combined OC and HRT use and two cohort studies on breastfeeding for 6 months. Second, this study calculated the risks not only for breast and ovarian cancer but also for endometrial and cervical cancer, highlighting that hormone factors were 1.02%, while the PAF of reproductive factors was 2.67% in 2020. Lastly, the contribution of postmenopausal HRT has been estimated using only EP-combined HRT, which is commonly used in women; however, this study subdivided the types of HRT and calculated the PAFs of each type of HRT, which is the novelty of this study.

The limitations of this study are as follows. First, there

is a lack of cohort studies based on Korean populations to measure the risks of ovarian, endometrial, and cervical cancers. Therefore, to supplement the RRs of female-related cancers, this study estimated the risks based on Asian and Global populations as substitutes. Second, there is a potential for measurement bias in the process of estimating the association between six months of breastfeeding and the risk of breast cancer. Based on adequate breastfeeding exposure, the final estimated risks were derived using the proportions of each risk estimate. By using the KNHANES as the source of exposure data, which is self-reported, may lead to information bias, specifically recall-bias. The 'unknown' response could result in missing data, potentially leading to incomplete or biased estimates for the exposures-disease relationship. However, we compared various sources of exposure data, and among them KNHANES was selected as it had the least amount of missing data, making it the most suitable for exposure data.

Additionally, when negative values were obtained in the lower confidence interval while estimating the PAF, the value was arbitrarily set to 0.00% as it was not valid for ACs to have negative values. Lastly, the value of PAF varies according to the prevalence of risk factors based on Levin's formula. Various data sources were compared to estimate the prevalence of carcinogenic factors, including health insurance statistics and the KNHANES from the Korea Statistical Information Service (KOSIS). Health insurance statistics from the KOSIS were considered appropriate for reflecting prevalence, as the survey was conducted on individuals covered by health insurance and represented a large portion of the population. However, most of the data were from the latter half of 2010, which may have resulted in an overestimation due to insufficient data for the 10-year period.

Through this study, the PAF for hormone and reproductive factors in Korean women were calculated, with hormone contributed 1.02% and reproductive accounted for 2.67% in 2020. Therefore, based on the definition of PAF, 1.02% of female cancers can be prevented by not using combined OC or any types of HRT. Among reproductive factors, breastfeeding for more than 6 months suggest to prevent approximately 2.67% of female cancer, typically to breast cancer. The results of this study can be used as evidence-based value to inform the recommendations for women. Breastfeeding is one of the dilemmas for working mothers in Korea. While they may want to breastfeed for their child's sake, they may choose to stop breastfeeding early due to low milk supply, body shape concerns, or the need of quickly returning back to their workplaces. However, breastfeeding can be recommended not only for the child's benefit but also for reducing the mother's future cancer risks by showing its impacts of this study. Additionally, for hormone use, it serves as a new guideline to recommend discontinuing long-term use of OC, taken for contraception rather than treatment purpose based on the study indicators. Lastly, among four selected female cancers, breast cancer was observed to be a significant level of prevention. It could serve as a foundation for recommending more frequent breast cancer screening to younger women, rather than limiting to women over 40 years old with every two years of the national cancer screening program.

Furthermore, if future cohort studies of female cancer and reproductive/hormone factors among Koreans increase, estimating PAF based on the duration of hormone use, rather than simply whether use or not, would likely provide more useful evidence for clinical practice. Considering that the number of child births is a modifiable reproductive factor, if the differences between pregnancy experience and childbirths experience are clearly distinguished in the data and the associated risk for female cancers is calculated accordingly, this could be one of the factors included in future studies.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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The prevalence rates of risk factors were used with the data provided by the Korea National Institute of Health (KNIH), Korea Disease Control and Prevention Agency (KDCA), and the Occupational Safety and Health Research Institute (OSHRI), Korea Occupational Safety and Health Agency (KOSHA), and the Korean Statistical Information Service (KOSIS).

The incidence and mortality rates of cancers were used with the data provided by the Cancer Registration Statistics, Korea National Cancer Center (KNCC), and the Korean Statistical Information Service (KOSIS).

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References

1. World Health Organization. Combined estrogen progestogen contraceptives and combined estrogen progestogen menopausal therapy. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 91 [Internet]. International Agency for Research on Cancer; 2007 [cited 2021 Nov 1]. Available from: https://publications.iarc.fr/109
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Pharmaceuticals. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt A):1-401.
3. Lactation and the risk of cancer [Internet]. World Cancer Research Fund/American Institute for Cancer Research; 2018 [cited 2025 Feb 20]. Available from: https://www.wcrf.org/preventing-cancer/topics/breastfeeding-and-cancer/
4. Shin HR, Park S, Shin A, Jung KW, Park B, Choi KS, et al. Attributable causes of cancer in Korea in the year 2009. National Cancer Center; 2009.
5. Park B, Park S, Shin HR, Shin A, Yeo Y, Choi JY, et al. Population attributable risks of modifiable reproductive factors for breast and ovarian cancers in Korea. BMC Cancer. 2016;16:5.
6. Park H, Kim K. Trends and factors associated with oral contraceptive use among Korean women. Healthcare (Basel). 2021;9:1386.
7. Huh Y, Kim YN, Kim YS. Trends and determinants in breastfeeding among Korean women: a nationwide population-based study. Int J Environ Res Public Health. 2021;18:13279.
8. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 100. A review of human carcinogens. International Agency for Research on Cancer; 2007.
9. World Cancer Research Fund, American Institute for Cancer Research. Recommendations and public health policy implications. Continuous update project expert report 2018. World Cancer Research Fund, American Institute for Cancer Research; 2018.
10. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002;360:187-95.
11. Soerjomataram I, Shield K, Marant-Micallef C, Vignat J, Hill C, Rogel A, et al. Cancers related to lifestyle and environmental factors in France in 2015. Eur J Cancer. 2018;105:103-13.
12. Yeo JH, Kim EY. Social policies and breastfeeding duration in South Korea: a survival analysis of the national data. Midwifery. 2022;107:103282.
13. Lee S, Ko KP, Lee JE, Kim I, Jee SH, Shin A, et al. The Korea Cohort Consortium: the future of pooling cohort studies. J Prev Med Public Health. 2022;55:464-74.
14. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open. 2017;7:e016640.
15. Yoo KY, Shin HR, Chang SH, Lee KS, Park SK, Kang D, et al. Korean multi-center cancer cohort study including a biological materials bank (KMCC-I). Asian Pac J Cancer Prev. 2002;3:85-92.
16. Kweon SS, Shin MH, Jeong SK, Nam HS, Lee YH, Park KS, et al. Cohort profile: the Namwon study and the Dong-gu study. Int J Epidemiol. 2014;43:558-67.
17. Jee YH, Emberson J, Jung KJ, Lee SJ, Lee S, Back JH, et al. Cohort profile: the Korean Cancer Prevention Study-II (KCPS-II) Biobank. Int J Epidemiol. 2018;47:385-6f.
18. Kim J. Cancer screenee cohort study of the National Cancer

Center in South Korea. Epidemiol Health. 2014;36:e2014013.
19. Lee C, Choe EK, Choi JM, Hwang Y, Lee Y, Park B, et al. Health and Prevention Enhancement (H-PEACE): a retrospective, population-based cohort study conducted at the Seoul National University Hospital Gangnam Center, Korea. BMJ Open. 2018;8:e019327.
20. Rhee EJ, Park SE, Chang Y, Ryu S, Lee WY. Baseline glycemic status and mortality in 241,499 Korean metropolitan subjects: a Kangbuk Samsung Health Study. Metabolism. 2016;65:68-77.
21. Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9:531-41.
22. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105 Suppl 2:S77-81.
23. Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi L, Bain CJ, et al. Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Aust N Z J Public Health. 2015;39:477-84.
24. Grundy A, Poirier AE, Khandwala F, Grevers X, Friedenreich CM, Brenner DR. Cancer incidence attributable to lifestyle and environmental factors in Alberta in 2012: summary of results. CMAJ Open. 2017;5:E540-5.
25. Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T, et al. Attributable causes of cancer in Japan in 2005: systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. Ann Oncol. 2012;23:1362-9.
26. Seo SH. Low fertility trend in the Republic of Korea and the problems of its family and demographic policy implementation. Popul Econ. 2019;3:29-35.
27. Lee SY, Kim MT, Kim SW, Song MS, Yoon SJ. Effect of lifetime lactation on breast cancer risk: a Korean women's cohort study. Int J Cancer. 2003;105:390-3.