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Menstrual factors and cancer risk among Korean women

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Background It has been suggested that lifetime exposure to female hormones is related to cancer risk in women. The authors investigated the association between age at menarche and menopause and cancer risk in a prospective study of Korean women.

Methods A total of 443 909 women, in the age group of 30–80 years in the 1993–94 time period were included in the analysis. During 12 years of follow-up, 17 959 incident cancer cases were identified by record linkage to the Central Cancer Registry database.

Results Early age at menarche was associated with an increased risk of breast cancer and a decreased risk of stomach and gallbladder cancer. Later age at menopause was associated with an increased risk of breast cancer. When the analysis was restricted to postmenopausal women, the associations of age at menarche and menopause with cancers of the breast, stomach and gallbladder persisted.

Conclusion These findings suggest that female hormonal factors play a significant role in the development of cancer in Korean women.

Keywords Menstruation, neoplasms, risk factor

Introduction

In the classic estimation of causes of cancer by Doll and Peto,[1] reproductive and sexual behaviours were suggested to account for 7% of the mortality of cancer in the USA. In a recent report for attributable causes of cancer in France in the year 2000 project by the International Agency for Research on Cancer (IARC) Working Group, reproductive factors were responsible for 1.1% of cancer deaths in women.[2] Although cancers of the breast, ovary and uterine corpus were the most representative cancers that were influenced by reproductive factors in those reports, other cancers, such as cancer of the stomach,[3–6] colorectum,[7–10] lung,[11–14] pancreas[15] and thyroid[16–19] have also been suggested to be associated with female hormonal factors.

Among the female hormonal factors, menstrual factors such as age at menarche and age at menopause are likely to be associated with cancers at sites other than reproductive organs, given that those two factors are affected by nutritional status as well as socio-economic status during childhood and adulthood.[20,21] The associations between age at menarche and menopause and breast cancer risk have been shown to be similar in Asian women, including Korean women[22,23] to those in Western women. However, the associations between the menstrual factors and the risk of cancers other than of reproductive organs have not been well elucidated. Indeed, the findings between studies have been inconsistent, especially for the direction of the association. For example, later age at menarche is associated with either increased[24] or decreased[25] risks for gallbladder cancer, and is associated with a decreased risk for lung cancer,[13] whereas other studies showed no association between age at menarche and lung cancer risk in women.[11,12] Moreover, little is known regarding the associations between age at menarche and menopause and cancers in Asian women.

In this regard, we investigated the association of age at menarche and menopause with total and site-specific cancer risks in a cohort of Korean women. Korean women have experienced rapid secular changes in their menstrual and reproductive patterns during the last few decades. Women in the 1980 birth cohort experienced menarche at a younger age and menopause at a later age compared with the 1900 birth cohort.[26] As the same transition could occur in other populations of Asian women in developing countries, clarification of the associations between cancers and reproductive patterns in Korean women would give better insight into the future trends in cancer incidence in populations who experience similar changes.

Materials and methods

The study participants were Korean women who were employed as public servants or female dependants of public servants who had undergone a health examination provided by the Korea Medical Insurance Corporation between 1993 and 1994. Among 504 058 women aged between 30 and 80 years at baseline, 10 073 participants who were diagnosed with cancer prior to 1993 were excluded. Women in whom the information on age at menarche (50 076 women) was unavailable were also excluded. Finally, a total of 443 909 women were included in the analysis.

Information on health-related behaviours and the menstrual and reproductive histories of participants was obtained using a self-administered questionnaire. With respect to health-related behaviours, cigarette smoking habits (never smoker, ex-smoker, current smoker or unknown), alcohol consumption (yes, no or unknown) and engagement in regular exercise (yes, no or unknown) were assessed. For menstrual and reproductive factors, information on age at menarche ($\leqslant$14, 15–16 or $\geqslant$17 years), age at first live birth (<26, 26–29, $\geqslant$30 years or nulliparous), use of oral contraceptives (ever or never), menopausal status (pre-menopausal or post-menopausal), age at menopause (<45, 45–49, 50–54 or $\geqslant$55), reasons for menopause (natural, surgical, radiotherapy/medication or unknown), use of hormone replacement therapy (ever or never) and breastfeeding (ever or never) was collected. We defined post-menopausal status as follows: self-report of natural menopause ($n = 177\,546$), use of hormonal replacement therapy ($n = 7098$), or $\geqslant$55-year-old women ($n = 14\,159$). The age criteria for post-menopausal status were based on a nationwide Korean study.[27] Socio-economic status was classified into three groups (low, middle or high) based on the tertile distribution of the monthly salary level of the women public servants or the family dependants for those women who were unemployed. Height and weight were measured according to a standardized protocol. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in metres squared and was categorized into four groups (<20, 20–22.9, 23–24.9 or $\geqslant$25 kg/m^2).

Participants were followed by data linkage to the Central Cancer Registry for cancer occurrence and the Korean National Statistical Office for death from 1 October 1994 to 31 December 2004. Associations of age at menarche and age at menopause with cancer at overall and specific sites were estimated using a Cox proportional hazard model with an adjustment for age, BMI, socio-economic status, cigarette smoking, alcohol consumption, menopausal status, age at the first live birth and breastfeeding. For specific cancers, we selected 10 most common cancers based on cancer registry data of Korean women in 2004.[28] For post-menopausal women, the reason for menopause and age at menopause were additionally adjusted. In cases with missing values for the variables included in the analysis model, a dummy category was assigned to the missing value. To determine whether or not the trend of associations across age at menarche and age at menopause was significant, the order of the age categories was treated as a continuous variable in the Cox proportional hazard model. This study was approved by the Institutional Review Board of Samsung Medical Center in Seoul, Korea.

Results

During 11.8 years of follow-up (5 224 750 person-years), a total of 17 959 cancer cases were documented. Gastric cancer (3021 cases) was the most common cancer, followed by breast cancer (2853 cases) and colorectal cancer (2153 cases). Among 234 819 post-menopausal women at baseline, 12 018 cancer cases were identified during follow-up.

Table 1 shows the distribution of demographic characteristics, menstrual and reproductive histories and other risk factors for cancer among all the study participants and among the post-menopausal participants. Of the total participants, 45% were post-menopausal women at baseline. Mean age of the participants was 62.4 years. Among all participants, only 3.4 % were current smokers, 13.9% were regular alcohol drinkers, 27.2% had BMI $\geqslant$25 kg/m^2, 21% had menarche before 14 years of age, 40.3% had a first live birth before 25 years of age and 55.5% had ever breastfed. Among post-menopausal women, 6.3% were current smokers, 12.8% were regular alcohol drinkers, 35.7% were obese, 10.1% had menarche before 14 years of age, 58.4% had a first live birth

Table 1 Baseline characteristics of the study participants

Characteristics	All women ($N = 443\,909$) n (%)	Post-menopausal women ($N = 198\,803$) n (%)
Age at baseline (years)		
30–39	99 421 (22.4)	968 (0.5)
40–49	144 753 (32.6)	17 576 (8.8)
50–59	120 529 (27.2)	101 053 (50.8)
⩾60	79 206 (17.8)	79 206 (39.9)
Monthly salary		
Low	117 470 (26.5)	59 492 (29.9)
Middle	140 869 (31.7)	51 823 (26.1)
High	185 570 (41.8)	87 488 (44.0)
BMI (kg/m^2)		
<20	57 044 (12.8)	18 618 (9.4)
20–22.9	159 172 (35.9)	57 257 (28.8)
23–24.9	106 976 (24.1)	51 862 (26.1)
⩾25	120 717 (27.2)	71 066 (35.7)
Cigarette smoking		
Never smoker	392 076 (88.3)	164 577 (82.8)
Ex-smoker	10 618 (2.4)	7 609 (3.8)
Current smoker	14 891 (3.4)	12 507 (6.3)
Unknown	26 324 (5.9)	14 110 (7.1)
Regular alcohol drinking		
No	371 102 (83.6)	166 344 (83.7)
Yes	61 668 (13.9)	25 550 (12.8)
Unknown	11 139 (2.5)	6 909 (3.5)
Age at menarche (years)		
⩽14	93 321 (21.0)	20 162 (10.1)
15–16	187 703 (42.3)	72 528 (36.5)
⩾17	162 885 (36.7)	106 113 (53.4)
Age at the first live birth (years)		
⩽25	179 046 (40.3)	116 191 (58.4)
26–29	159 642 (36.0)	41 165 (20.7)
⩾30	43 555 (9.8)	9 091 (4.6)
Nulliparous	61 666 (13.9)	32 356 (16.3)
Breastfeeding	246 451 (55.5)	113 307 (57.0)
Age at menopause (years)		
<45		23 295 (11.7)
45–49		59 310 (29.8)
50–54		78 816 (39.6)
⩾55		16 140 (8.1)
Unknown		21 242 (10.7)

before 25 years of age and 57% had ever breastfed. There was a clear shift of age at menarche across the birth cohort. The younger birth cohort had menarche at a younger age compared with the older birth cohorts; the trend was statistically significant ($P < 0.001$, data not shown).

Table 2 shows the association between age at menarche and overall, and site-specific cancers in all participants. Earlier age at menarche was associated with an increased risk for overall cancer compared with later age at menarche. A strong inverse association was observed between age at menarche and breast cancer risk (P for trend <0.001). In contrast, earlier age at menarche was associated with a decreased risk for gastric (P for trend <0.001) and gallbladder cancer (P for trend $= 0.01$). Women who had menarche at < 15 years of age had a 17% decreased risk for gastric cancer, a 37% decreased risk for gallbladder cancer and a 52% increased risk for breast cancer compared with women who had menarche at >16 years of age. However, there was no significant association between age at menarche and cancers at other sites, including the ovary.

Table 3 shows the association of age at menarche and age at menopause with overall and site-specific cancers in post-menopausal women at baseline. Associations between age at menarche and the risks of breast, stomach and gallbladder cancers persisted even in the analysis restricted to post-menopausal women. There was a positive association between age at menopause and breast cancer risk. Women who had menopause at >55 years of age had an 80% increased risk for breast cancer compared with women who had menopause at <45 years of age. The risk for cancers other than breast cancer was not associated with age at menopause.

Since the younger birth cohort experienced menarche at a younger age compared with the older birth cohorts, age-stratification was done to exclude possible cohort effect on the association between age at menarche and cancer risks. Age-stratification did not change the results (data not shown).

Discussion

In this large-size cohort study of Korean women, we reconfirmed that earlier age at menarche and later age at menopause were associated with an increased risk for breast cancer. We also found that earlier age at menarche was associated with a decreased risk for gastric and gallbladder cancer.

It has been suggested that age at menarche is affected by nutritional status during childhood,[20,29] and age at menopause is also affected by socio-economic circumstances, as well as nutritional status during childhood and adulthood.[21,30] A decline in the mean age at menarche has been observed not only in Korea,[26] but also in the USA[31] and European countries.[32] Although genetic effects explain 70–80% of the

Table 2 Associations[a] between the age at menarche and the risk of 10 major cancers

	Age at menarche (years)						
	<15 (n = 93 321)		15–16 (n = 187 703)		⩾17 (n = 162 885)		
Cancer sites	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	***P* trend**[†]
All cancers	2921	1.05 (1.00–1.10)	7347	1.04 (1.01–1.08)	7691	1.00 (Referent)	0.29
Stomach	360	0.83 (0.73–0.93)	1177	0.96 (0.89–1.04)	1484	1.00 (Referent)	0.001
Colorectum	282	0.98 (0.86–1.13)	843	0.99 (0.91–1.09)	1028	1.00 (Referent)	0.83
Colon	160	1.04 (0.86–1.25)	436	0.97 (0.85–1.10)	538	1.00 (Referent)	0.51
Rectum	124	0.91 (0.74–1.12)	424	1.05 (0.92–1.19)	500	1.00 (Referent)	0.25
Liver	133	0.90 (0.74–1.09)	509	1.07 (0.95–1.21)	624	1.00 (Referent)	0.13
Pancreas	59	1.16 (0.89–1.56)	199	1.12 (0.93–1.35)	248	1.00 (Referent)	0.49
Gallbladder	52	0.63 (0.47–0.85)	229	0.85 (0.72–1.00)	355	1.00 (Referent)	0.01
Lung	172	1.07 (0.90–1.28)	520	1.01 (0.89–1.13)	690	1.00 (Referent)	0.42
Breast	819	1.52 (1.36–1.70)	1272	1.24 (1.13–1.36)	762	1.00 (Referent)	<0.001
Uterine cervix	225	0.96 (0.81–1.13)	648	1.14 (1.02–1.28)	604	1.00 (Referent)	0.10
Ovary	110	1.14 (0.88–1.48)	214	1.03 (0.84–1.26)	190	1.00 (Referent)	0.32
Thyroid	327	1.10 (0.94–1.29)	629	1.06 (0.94–1.21)	472	1.00 (Referent)	0.39

[a]Hazard ratios (HR) and 95% confidence intervals(CI) were estimated with an adjustment for age, BMI, income level, alcohol consumption, cigarette smoking, menopausal status, age at the first live birth and breastfeeding.
[†]*P*-values for trend were obtained using Cox proportional hazard models in which the order of age at menarche category was treated as a continuous variable.

variance in pubertal timing, environmental influences may explain the worldwide secular changes in age at menarche.[33] Early menarche increases the risk of hormone-related cancers by extending reproductive years and consequent lifetime exposure to estrogen. In addition, age at menarche might be a proxy measure for early nutritional status. When total energy intake is considered, girls who consume more animal protein at the age of 3–5 years had earlier menarche in a longitudinal study of 67 Caucasian girls,[34]and girls who had higher fat intake showed earlier menarche in another longitudinal study of 261 girls in the age group of 8–15 years at baseline.[35]

It has been reported that adverse socio-economic circumstances in childhood and adulthood, such as living in a house without a bathroom,[21] a low level of education and manual social class[21,36] are associated with an earlier age at menopause. Women who were exposed to severe caloric restriction during the 1944–1945 Dutch famine had natural menopause 0.36 years earlier than those who were not exposed to the famine, and famine exposure during early childhood was an important factor leading to an earlier age at menopause.[30] Higher intakes of total calories, fruits, protein,[37] fat, cholesterol, coffee and calcium[38] are associated with later menopause in Chinese and Japanese women, although an intervention with a low-fat, high-carbohydrate diet did not result in a significant change in the timing of menopause in a 7-year follow-up study with 2611 women.[39]

Given the influence of environmental factors on the age at menarche and menopause, a significant association of age at menarche and menopause with cancer would support hormonal or nutritional factors in the development of cancer. For breast cancer, it is well known that hormonal and reproductive factors are closely associated with breast cancer risk, even in Asian women.[22] The increased risk of breast cancer associated with earlier age at menarche and later age at menopause confirmed previously reported associations between lifetime estrogen exposure and breast cancer risk.[40]

A positive association has been observed between estimates of a woman's lifetime number of ovulations and ovarian cancer risk,[41] and it could be hypothesized that earlier age at menarche and later age at menopause might increase the risk of ovarian cancer by increasing the number of ovulations. However, the current study showed that age at menarche and age at menopause were not associated with the risk for ovarian cancer, which is generally consistent with previous studies that showed no association with age at menarche or age at menopause.[42–44]

Interestingly, we found that early menarche was associated with a reduced risk for gastric cancer. Although mortality from gastric cancer has decreased over the last three decades, gastric cancer used to be the most common incident cancer among Korean women until 2001, and it is still the third most common cancer in Korean women.[45] Although *Helicobacter*

Table 3 Associations[a] of the age at menarche and age at menopause with 10 major cancers in post-menopausal women

	Age at menarche (years)							**Age at menopause (years)**										
	<15 ($n=20\,162$)		15–16 ($n=72\,528$)		≥17 ($n=106\,113$)			<45 ($n=23\,311$)		45–49 ($n=59\,556$)		50–54 ($n=79\,872$)		≥55 ($n=16\,952$)		Unknown ($n=19\,112$)		
Cancer sites	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	***P* trend**†	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	Number of events	HR (95% CI)	***P* trend**‡
All cancers	1088	1.03 (0.96–1.10)	4192	1.05 (1.01–1.09)	5925	1.00 (Referent)	0.81	1333	1.00 (Referent)	3294	0.99 (0.93–1.06)	4592	1.02 (0.96–1.08)	1067	1.03 (0.95–1.12)	919	0.89 (0.81–0.97)	0.18
Stomach	171	0.82 (0.70–0.97)	800	0.97 (0.89–1.06)	1243	1.00 (Referent)	0.02	269	1.00 (Referent)	633	0.96 (0.84–1.11)	924	1.05 (0.91–1.20)	220	1.04 (0.87–1.25)	168	0.83 (0.68–1.01)	0.22
Colorectum	149	1.02 (0.85–1.21)	588	1.05 (0.94–1.17)	829	1.00 (Referent)	0.96	198	1.00 (Referent)	455	0.92 (0.77–1.08)	639	0.93 (0.79–1.09)	145	0.91 (0.73–1.13)	129	0.87 (0.69–1.09)	0.48
Colon	78	1.01 (0.79–1.29)	307	1.04 (0.90–1.20)	431	1.00 (Referent)	0.96	103	1.00 (Referent)	232	0.89 (0.71–1.13)	339	0.94 (0.75–1.18)	79	0.94 (0.70–1.27)	63	0.80 (0.58–1.11)	0.94
Rectum	73	1.03 (0.80–1.32)	291	1.07 (0.92–1.25)	408	1.00 (Referent)	0.99	98	1.00 (Referent)	230	0.94 (0.74–1.19)	310	0.91 (0.72–1.15)	68	0.87 (0.64–1.19)	66	0.92 (0.67–1.27)	0.34
Liver	85	0.97 (0.77–1.22)	371	1.08 (0.95–1.24)	521	1.00 (Referent)	0.55	134	1.00 (Referent)	295	0.88 (0.72–1.09)	370	0.80 (0.65–0.97)	99	0.92 (0.71–1.19)	79	0.78 (0.59–1.04)	0.14
Pancreas	40	1.07 (0.76–1.50)	171	1.14 (0.93–1.39)	226	1.00 (Referent)	0.94	56	1.00 (Referent)	130	0.96 (0.70–1.32)	183	0.99 (0.73–1.34)	37	0.81 (0.53–1.23)	31	0.74 (0.48–1.16)	0.51
Gallbladder	31	0.57 (0.39–0.82)	190	0.89 (0.74–1.06)	315	1.00 (Referent)	0.005	53	1.00 (Referent)	165	1.28 (0.94–1.75)	217	1.23 (0.91–1.66)	43	0.99 (0.66–1.48)	58	1.48 (1.01–2.17)	0.96
Lung	112	1.14 (0.93–1.39)	403	1.03 (0.91–1.17)	595	1.00 (Referent)	0.24	146	1.00 (Referent)	326	0.94 (0.78–1.15)	449	0.98 (0.81–1.18)	107	0.97 (0.75–1.25)	84	0.80 (0.61–1.06)	0.95
Breast	145	1.76 (1.44–2.14)	368	1.37 (1.18–1.58)	361	1.00 (Referent)	<0.001	69	1.00 (Referent)	239	1.27 (0.97–1.66)	404	1.58 (1.22–2.05)	83	1.80 (1.31–2.49)	79	1.23 (0.88–1.71)	<0.001
Uterine cervix	77	1.00 (0.78–1.27)	333	1.15 (0.99–1.32)	436	1.00 (Referent)	0.59	98	1.00 (Referent)	264	1.07 (0.84–1.34)	354	1.04 (0.83–1.31)	71	0.96 (0.71–1.31)	59	0.75 (0.54–1.04)	0.95
Ovary	28	1.14 (0.75–1.73)	91	1.03 (0.79–1.36)	124	1.00 (Referent)	0.56	27	1.00 (Referent)	69	1.00 (0.64–1.56)	103	1.13 (0.73–1.73)	24	1.21 (0.69–2.11)	20	0.85 (0.47–1.54)	0.33
Thyroid	69	1.02 (0.78–1.34)	195	0.89 (0.74–1.07)	290	1.00 (Referent)	0.56	55	1.00 (Referent)	164	1.11 (0.82–1.51)	224	1.12 (0.83–1.52)	43	1.10 (0.73–1.64)	68	1.53 (1.06–2.20)	0.58

[a]HRs and 95% CIs were estimated with an adjustment for age, BMI, income level, alcohol consumption, cigarette smoking status, age at first live birth and breastfeeding.
†*P*-values for trend were obtained using Cox proportional hazard models in which the order of age at menarche category was treated as a continuous variable.
‡*P*-values for trend were obtained using Cox proportional hazard models in which the order of age at menopause category was treated as a continuous variable after excluding subjects with missing information for age at menopause.

pylori infection is the most important risk factor for gastric cancer, hormonal factors have also been suggested to affect individual susceptibility to gastric cancer development. Expression of steroid hormonal receptors in normal and cancerous gastric tissues, a higher incidence of gastric cancer after carcinogen exposure in male rats than female rats, a reduced risk of developing gastric cancer in prostate cancer patients treated with estrogen and an association of gastric cancer with menstrual factors in epidemiological studies support a hormonal hypothesis for gastric cancer risk.[3] A study showed that the age-specific male:female ratio of the gastric cancer incidence rate increased gradually with a peak at age 60 years and decreased thereafter.[46] This pattern was unique, compared with that of other gastrointestinal cancers and repeatedly observed across several countries, suggesting that female sex hormones may play a protective role against gastric cancer. In addition, earlier age at menarche may reflect better socio-economic or nutritional condition during childhood, which relate to lower risk for *H. pylori* infection.[47] However, information that reflects childhood environment such as number of siblings, housing conditions and drinking water source was not available in the current study. Few studies have investigated the risk of gallbladder cancer in relation to female hormonal factors. In a small-scale case–control study, later age at menarche was associated with a higher risk of gallbladder cancer, which is in agreement with our results.[24] However, another study did not find the same association,[25] thus further study is necessary to clarify the association.

Women are suggested to be more susceptible than men to tobacco-induced carcinogenesis and may have a higher risk than men for developing lung cancer from smoking.[48] Estrogen receptors are present in normal and neoplastic lung tissues, and it has been suggested that female hormonal factors may play a role in lung carcinogenesis.[49,50] However, epidemiological evidence is inconclusive. Later age at menarche was associated with a decrease in lung cancer risk in our study and a case–control study,[13] whereas other studies reported no association.[11,12,51] Therefore, the role of female reproductive factors in lung cancer risk is still unclear and more study will be needed.

The current study has several strengths. The large sample size and long-term follow-up allowed an evaluation of the association between female menstrual factors and risk of cancer at diverse sites, including relatively rare cancers, such as gallbladder cancer, which have not been thoroughly studied. A wide range of covariates, including socio-economic status, BMI and height, were considered.

There were some limitations which should be considered. First, a lack of repeated measures for menstrual factors in study questions is one such limitation, however, the reliability of a questionnaire survey in Korean women to obtain information on menstrual and reproductive histories has been reported to be in an acceptable range.[52] The information was collected prospectively, therefore misclassification of information seems to dilute the possible association for cancer risk. Secondly, some women who were pre-menopausal at baseline may have entered the menopause during follow-up. We tried to overcome this problem by limiting analysis to post-menopausal women at the time of the baseline questionnaire. Thirdly, a substantial number of women were excluded from the analysis due to the lack of information about age at menarche (~10% of total participants) or menopausal age (20% of menopausal women), which might have caused biased results. However, we think this exclusion of subjects could have caused more conservative findings on the association between cancers and menstrual factors rather than inflated results, given the association of socio-economic factors with breast cancer risk and menstrual factors. Fourthly, we could not assess perimenopausal status due to the lack of information about the last menstrual period and female reproductive hormones, which might have caused misclassification bias. Fifthly, the information on some risk factors for cancer included in the final regression models, such as smoking and alcohol consumption, was not available in some participants. However, the proportion of participants with missing information was not high (5.9% for cigarette smoking and 2.5% for alcohol consumption) and significant bias seems less likely. Sixthly, completeness of outcome conformation can also be a source of biased results. The completeness of the Korea National Cancer Incidence database is reported to be 94.6%,[53] which is high enough not to cause significant bias in our study.

In conclusion, the findings of the current study that age at menarche and age at menopause are associated with cancers of the breast, stomach and gallbladder suggest that female hormonal factors play a significant role in the development of cancer in Korean women. Increase in breast cancer mortality and decrease in stomach cancer mortality in Korea[54] may be partly influenced by the changes in distribution of female hormonal factors of Korean women. As the secular trend in age at menarche or menopause among in Korean women is also observed in other Asian women populations who are experiencing rapid socio-economic transition, the findings of the current study may provide further insight to the prediction of cancer patterns in those countries.

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KEY MESSAGES

- Korean women as well as Asian women who live in countries with rapid socio-economical transition experience changes of age at menarche and menopause.
- In the current study, early menarche and late menopause were associated with an increased risk of breast cancer and early menarche was associated with a decreased risk of stomach and gallbladder cancer in 443 909 women during 12 years of follow-up.
- Secular changes in female reproductive factors may contribute to changes in female cancer patterns.

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