ORIGINAL RESEARCH

Prediagnosis obesity and secondary primary cancer risk in female cancer survivors: A national cohort study

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Abstract

Background: This study evaluated the effects of body mass index (BMI) before the diagnosis of the first primary cancer on the development of secondary primary cancers (SPCs) in female cancer survivors.

Methods: This study population included 146 377 Korean female cancer survivors whose first primary cancer was diagnosed between 2002 and 2010. The incidence of SPCs was evaluated throughout follow‐up until December 2011. We used Cox proportional hazards models to calculate the hazard ratios of SPCs with prediagnosis BMI and compared it to those of first cancers in the general population.

Results: After 565 877 person‐years of follow‐up, 2222 patients with SPC were observed. The higher BMI was more in female cancer survivors than in general population. The age‐standardized incidence rate of cancer in cancer survivors was 2.02 times higher than that of the general population. There were positive linear trends between prediagnosis BMI and risk of overall, colorectal, ovary, thyroid, and obesity‐related SPCs. In addition, the BMI‐SPC risk association was statistically significant in female cancer survivors without smoking history (P_trend = 0.001) and with a localized first primary cancer (P_trend = 0.014). However, the magnitude of the
1 | INTRODUCTION

The increasing number of cancer survivors has resulted from early cancer detection and advances in cancer treatment. However, many cancer survivors also have an increased risk of secondary primary cancers (SPCs), which might be greater than the risk of primary cancers in the general population. A recent study reported that mortality due to SPCs was higher than mortality due to first primary cancer. SPCs have been associated with genetic susceptibility, the carcinogenic effects of cancer treatment, and the influence of behavioral risk factors such as smoking and alcohol intake.

Obesity is a well-known risk factor for cancer in the general population including cancers of the colon, lower esophagus, kidney, gallbladder, breast, and endometrium. In addition, several studies have reported the association between obesity and increased SPC risk at specific sites such as breast and colorectum. Although the mechanisms of the linkage between obesity and cancer risk have not been fully elucidated, hormones, including sex hormones, have been associated with increased cancer risk. Therefore, it would be relevant to evaluate the correlation between obesity and cancer risk separately according to sex. Previously, we reported that obesity was associated with increased primary cancer risk and SPC risk in Korean male survivors. These studies demonstrated that male cancer survivors who had a higher prediagnosis BMI had an increased risk of subsequent overall SPCs and that the magnitude of the association between obesity and SPC risk was stronger than that of first primary cancer risk. However, there was no study for evaluating it in female cancer survivors.

This study evaluated the association between prediagnosis BMI and SPC risk in female cancer survivors by analyzing merged data from the Korean National Health Insurance Service (NHIS) and Korea Central Cancer Registry (KCCR). We also compared the risk of SPC in obese female cancer survivors vs the risk of first primary cancers in the general population of women.

2 | METHODS

2.1 | Study population

This study included Korean female cancer survivors, who got health examinations by the NHIS before their first cancer diagnosis during January 2002 and December 2010. As previously mentioned, the Korean NHIS is the only public health insurer in Korea, and it provides biennial health examinations, including height and weight measurements and behavioral surveys, in which 68.2% of Koreans have been participated in 2010. The KCCR is a population-based national cancer registry that includes information on more than 95% of patients with newly diagnosed cancer in Korea.

This study was approved by the Institutional Review Board of the National Cancer Center, Korea (NCC2015-2017) and was exempt from the requirement of informed consent because the information in these datasets had been de-identified.

We identified 11,175,133 women who were 18 years of age or older and used the Korean NHIS at least once between 2002 and 2010. We then excluded female survivors without information on prediagnosis BMI (N = 8,295), who were diagnosed with thyroid cancer as the primary cancer (N = 57,881) and who were dying or diagnosed with their first incidence of cancer within 1 year after baseline NHIS examination (N = 146,572). Among the remaining 10,962,385 women, we selected 146,377 female cancer survivors with their first primary cancer diagnosed between 2002 and 2010. The primary endpoint of this study was a newly diagnosed SPC, defined as a cancer with a different topology using the International Classification of Diseases, Tenth Revision [ICD-10] at least 2 months later than the first primary cancer.

2.2 | Assessment of prediagnosis exposure and covariates

We collected health-related information from self-reported questionnaires including previous medical history, current health status, smoking, alcohol intake, diet, exercise, and family history. We obtained medical comorbidities, place of...
TABLE 1 Descriptive characteristics of the study population (2002-2010)

| Characteristic                              | Cancer survivors, prediagnosis (N = 146 377) | Total cohort, starting year (N = 10 962 385) |
|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                             | N    | %    | Person-years | N    | %    | Person-years |
| Mean age at inclusion, years (SD)           | 56.67 | 13.20 |              | 45.48 | 15.27 |              |
| Body mass index, kg/m²                      |      |      |              |      |      |              |
| Mean (SD)                                   | 23.92 | (3.28) |              | 23.03 | (3.37) |              |
| <18.5                                       | 4958  | 3.39  | 19168.65     | 711 713 | 6.49  | 3356729.01     |
| 18.6-22.9                                   | 54 277 | 37.08 | 210208.66    | 5 109 301 | 46.61 | 24053918.48    |
| 23-24.9                                     | 35 664 | 24.36 | 137567.21    | 2 277 630 | 20.78 | 10911422.97    |
| 25-29.9                                     | 45 268 | 30.93 | 175024.32    | 2 503 144 | 22.83 | 11938694.03    |
| ≥30                                         | 6210 | 4.24  | 23907.60     | 360 597 | 3.29  | 1576156.44     |
| Smoking status                              |      |      |              |      |      |              |
| Never                                       | 133 520 | 94.37 | 516219.76    | 10 034 872 | 94.02 | 47588054.11    |
| Former                                      | 1970 | 1.39  | 7493.62      | 197 109 | 1.85  | 827942.72      |
| Current                                     | 5999 | 4.24  | 22645.85     | 440 605 | 4.13  | 1760678.45     |
| Physical activity, times/wk                 |      |      |              |      |      |              |
| None                                        | 94 526 | 66.6  | 367694.19    | 6 959 224 | 65.09 | 33396605.00    |
| 1-2                                         | 22 934 | 16.16 | 88400.65     | 2 027 026 | 18.96 | 9171776.37     |
| 3-4                                         | 10 792 | 7.60  | 40465.94     | 914 394 | 8.55  | 3993948.33     |
| 5-6                                         | 3397 | 2.39  | 12686.45     | 288 919 | 2.70  | 1160115.76     |
| 7                                           | 10 291 | 7.25  | 39330.54     | 502 092 | 4.70  | 2622259.12     |
| Alcohol consumption, drinks/wk              |      |      |              |      |      |              |
| None                                        | 116 889 | 82.55 | 452813.03    | 7 532 414 | 71.59 | 36524753.81    |
| 2                                           | 22 061 | 15.58 | 86592.12     | 2 702 027 | 25.68 | 12536983.25    |
| 3-4                                         | 1543 | 1.09  | 5771.36      | 210 190 | 2.00  | 742838.12      |
| 5                                           | 1106 | 0.78  | 4193.93      | 76 747 | 0.73  | 314632.09      |
| Fasting serum glucose, mg/dL                |      |      |              |      |      |              |
| <100                                        | 122 143 | 83.65 | 475212.00    | 9 789 904 | 89.42 | 46427368.82    |
| 100-125                                     | 12 787 | 8.76  | 48081.44     | 677 834 | 6.19  | 3125487.46     |
| 126-139                                     | 3412 | 2.34  | 12706.44     | 161 958 | 1.48  | 724556.68      |
| ≥140                                        | 7672 | 5.25  | 28357.98     | 318 459 | 2.91  | 1469428.83     |
| Fasting serum cholesterol, mg/dL            |      |      |              |      |      |              |
| <200                                        | 76 163 | 52.17 | 293855.24    | 6 718 084 | 61.37 | 31590923.91    |
| 200-239                                     | 48 548 | 33.25 | 188448.25    | 3 065 740 | 28.01 | 14602741.86    |
| ≥240                                        | 21 293 | 14.58 | 82 086.69    | 1 162 189 | 10.62 | 5547547.08     |
| Presence of disability                      |      |      |              |      |      |              |
| No disability                               | 136 534 | 93.30 | 524107.63    |              |      |              |
| Disability                                  | 9803 | 6.70  | 41617.86     |              |      |              |
| Diabetes                                    | 30 499 | 20.84 | 119541.19    |              |      |              |
| Dyslipidemia                                | 37 024 | 25.3  | 151566.46    |              |      |              |
| Osteoporosis                                | 3686 | 2.52  | 15076.51     |              |      |              |
| Heart disease                               | 7616 | 5.2   | 29850.23     |              |      |              |
| Liver disease                               | 35 328 | 24.14 | 137972.55    |              |      |              |
| Cerebrovascular disease                     | 13 996 | 9.56  | 57541.04     |              |      |              |

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residence, and insurance level for evaluating about socioeconomic status using the NHIS database.

Prediagnosis information including height and weight was collected from the one follow-up cycle data before the primary cancer diagnosis. Height and weight were measured directly by trained persons. We calculated prediagnosis BMI and divided them by WHO criteria for Asian populations. A BMI with 18.6-22.9 kg/m² was categorized as normal, 23.0-24.9 as overweight, 25.0-29.9 as obese, and ≥30 as severely obese.31

2.3 | Statistical analysis

For each individual, the accumulated person-years of risk were calculated from the date of diagnosis of the first primary cancer to the date of diagnosis of a SPC, death, or last follow-up (31 December 2011), whichever came first. For comparing cancer incidence between female cancer survivors and the general women population, age-standardized incidence rates (IRs) were estimated using a direct standardization method. We used Cox proportional hazards analysis for calculating age-adjusted and multivariable-adjusted hazard ratios (aHRs) for SPC development related to prediagnosis BMI. We performed the tests for trends using median values for BMI.

In the additional sensitivity analyses, we excluded individuals diagnosed with simultaneous primary cancers within 2 years of the first cancer diagnosis for minimizing detection bias. We also analyzed data adjusted for follow-up time. We also stratified associations according to age at first cancer diagnosis, stage of first primary cancer (2006-2010), smoking, location of residence, insurance level, and disability status. In addition, we assessed the BMI-SPC risk association in survivors of an obesity-related cancer. Here, obesity-related cancers were defined as previously reported, dose-response cancers with obesity (esophageal, colorectal, pancreas, and renal cancer).24,32 In addition, obesity-related female cancers also were defined as obesity-related cancers, breast cancer, and endometrial cancer.

We also compared the strength of the association between BMI and risk of cancer in female cancer survivors vs general population using Cox proportional analysis. For the evaluation of first primary cancer risk, 10 816 008 women in general population who were seen by the Korean NHIS during 2002-2010 were included and exposure variables were collected from the first health examination that occurred in the same periods. Follow-up duration was from the date of the first health examination to the date of diagnosis of a first primary cancer, death, or last day of 2011, whichever came first. We calculated P values for heterogeneity using the Q statistic. To evaluate the potential impact of death as a competing risk, we used the Poisson regression method of Fine and Gray.33 We used SAS for statistical analysis (version 9.3; SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Clinical characteristics of the study population

Table 1 shows the clinical characteristics of the study population. The mean age of female cancer survivors and the total population at baseline was 56.7 years and 45.5 years, respectively. Although mean BMI was similar in both groups (23.9 in cancer survivors vs 23.0 in total population), the proportions of the obese population (BMI ≥ 25.0 kg/m²) were 35.2% (30.93% with 25.0-29.9 kg/m², 4.24% with ≥30.0 kg/m²) for cancer survivors vs 26.1% (22.83% with 25.0-29.9 kg/m², 3.29% with ≥30.0 kg/m²) for the total population.

3.2 | Age-Standardized IRs of first primary cancers and SPCs

Of 565 877 person-years of follow-up, 2222 patients developed SPCs. The most common site of SPC in female cancer survivors was the thyroid, which represented 32.76% of all SPCs, followed by cancers of the colorectum (11.16%), lung (10.40%), stomach (7.61%), and breast (5.67%) (Table 2).

The overall age-standardized IR of SPCs was 453.9 occurrences per 100 000 person-years, more than 2.02 times the risk of first primary cancers (224.8 per 100 000 person-years;
### TABLE 2  Age-standardized IRs of the first and second primary cancers

| Site                        | All first cancer | Second cancer | Body mass index <25 first cancer | Second cancer | Body mass index ≥25 first cancer | Second cancer |
|-----------------------------|------------------|---------------|----------------------------------|---------------|----------------------------------|---------------|
| All cancers, No.            | 146 377          | 2222          | 94 899                           | 1399          | 51 478                           | 823           |
| Age-standardized IR         | 224.77           | 453.89<sup>e</sup> | 221.34                           | 437.87<sup>e</sup> | 232.72                           | 577.31<sup>e</sup> |
| Stomach, No.               | 23 653           | 169           | 15 447                           | 113           | 8206                             | 56            |
| Age-standardized IR         | 36.48            | 26.44<sup>e</sup> | 36.84                            | 27.29<sup>e</sup> | 35.74                            | 40.9<sup>e</sup> |
| Colorectal, No.            | 22 649           | 248           | 13 923                           | 147           | 8726                             | 101           |
| Age-standardized IR         | 33.73            | 40.71<sup>e</sup> | 32.6                             | 38.18<sup>e</sup> | 35.89                            | 57.72<sup>e</sup> |
| Liver, No.                 | 8295             | 102           | 4965                             | 63            | 3330                             | 39            |
| Age-standardized IR         | 12.23            | 15.22<sup>e</sup> | 11.76                            | 14.21<sup>e</sup> | 13.24                            | 23.72<sup>e</sup> |
| Pancreas, No.              | 4497             | 60            | 2715                             | 37            | 1782                             | 23            |
| Age-standardized IR         | 7.05             | 6.53<sup>e</sup> | 6.85                             | 6.61<sup>e</sup> | 7.58                             | 6.96<sup>e</sup> |
| Lung, No.                  | 11 786           | 231           | 7799                             | 163           | 3987                             | 68            |
| Age-standardized IR         | 18.24            | 41.08<sup>e</sup> | 19.11                            | 44.56<sup>e</sup> | 16.55                            | 31<sup>e</sup> |
| Breast, No.                | 30 349           | 126           | 21 100                           | 80            | 9249                             | 46            |
| Age-standardized IR         | 48.18            | 26.19<sup>e</sup> | 47.21                            | 24.94<sup>e</sup> | 49.04                            | 31.19<sup>e</sup> |
| Uterine cervix, No.        | 6925             | 46            | 4634                             | 24            | 2291                             | 22            |
| Age-standardized IR         | 11.39            | 7.64<sup>e</sup> | 11.14                            | 6.46<sup>e</sup> | 11.83                            | 9.26<sup>d</sup> |
| Thyroid, No.               | 728              | 454           | 728                              | 454           | 274                              | 274           |
| Age-standardized IR         | 192.64           | 180.62        | 1333                             | 20            | 265.74                           | 20            |
| Lymphoma, No.              | 3886             | 41            | 2553                             | 21            | 1333                             | 20            |
| Age-standardized IR         | 6.15             | 4.86<sup>a</sup> | 6.1                              | 4.28<sup>a</sup> | 6.14                             | 5.75<sup>a</sup> |
| Ovary, No.                 | 4113             | 43            | 2746                             | 23            | 1367                             | 20            |
| Age-standardized IR         | 6.61             | 8.34<sup>d</sup> | 6.44                             | 7.51<sup>d</sup> | 7.04                             | 8.77<sup>d</sup> |
| Oral cavity and pharynx/Esophagus/ larynx, No. | 1894 | 38 | 1265 | 23 | 629 | 15 |
| Age-standardized IR         | 3.05             | 4.67<sup>e</sup> | 3.08                             | 4.82<sup>e</sup> | 3.18                             | 4.44<sup>e</sup> |
| Gallbladder and other biliary, No. | 4994 | 50 | 2926 | 32 | 2068 | 18 |
| Age-standardized IR         | 7.93             | 6.26<sup>e</sup> | 7.44                             | 5.6<sup>e</sup> | 8.98                             | 11.54<sup>e</sup> |
| Uterine corpus, No.        | 3587             | 49            | 2075                             | 31            | 1512                             | 18            |
| Age-standardized IR         | 5.17             | 11.93<sup>e</sup> | 4.36                            | 11.88<sup>e</sup> | 8.16                             | 8.02<sup>e</sup> |
| Kidney, No.                | 2314             | 37            | 1367                             | 24            | 947                              | 13            |
| Age-standardized IR         | 3.44             | 5.66<sup>e</sup> | 3.13                             | 5.78<sup>e</sup> | 4.23                             | 5.07<sup>e</sup> |
| Urinary bladder, No.       | 1421             | 23            | 883                              | 18            | 538                              | 5             |
| Age-standardized IR         | 2.25             | 4.14<sup>e</sup> | 2.21                             | 4.83<sup>e</sup> | 2.34                             | 1.52<sup>e</sup> |
| Leukemia, No.              | 2144             | 29            | 1438                             | 21            | 706                              | 8             |
| Age-standardized IR         | 3.64             | 6.37<sup>e</sup> | 3.57                             | 6.08<sup>e</sup> | 4                                 | 9.76<sup>e</sup> |
| Others, No.                | 13 870           | 202           | 9063                             | 125           | 4807                             | 77            |
| Age-standardized IR         | 22.42            | 48.65<sup>e</sup> | 22.57                            | 47.61<sup>e</sup> | 22.23                            | 59.82<sup>e</sup> |
| Obesity-related, No.<sup>b</sup> | 29 786 | 351 | 18 228 | 212 | 11 558 | 139 |
| Age-standardized IR         | 36.21            | 49.38<sup>e</sup> | 34.86                            | 46.83<sup>e</sup> | 39.22                            | 67.37<sup>e</sup> |
| Obesity-related female, No.<sup>c</sup> | 64 247 | 520 | 42 073 | 315 | 22 174 | 205 |
| Age-standardized IR         | 91.02            | 84.35<sup>e</sup> | 88.91                            | 79.77<sup>e</sup> | 94.63                            | 107.85<sup>e</sup> |

IR of cancer per 100 000 person-years. No. indicates the number of patients with first cancer and SPC.

IR, incidence rate.

*Not significant.

<sup>b</sup>Includes colorectal, kidney, pancreatic, and esophageal cancers.

<sup>c</sup>Includes colorectal, kidney, pancreatic, esophageal, breast, and urinary bladder cancers.

<sup>d</sup>P < 0.05

<sup>e</sup>P < 0.001
| Site of SPC     | Prediagnosis BMI, kg/m² | <18.5 | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | P<sub>trend</sub><sup>a</sup> |
|-----------------|-------------------------|-------|-----------|---------|---------|-----|------------------|
| All, No.        |                         | 56    | 772       | 571     | 719     | 104 |                  |
| Age-adjusted HR |                         | 0.82  | 1.13      | 1.14    | 1.24    | 1.24 | < 0.001          |
| 95% CI          |                         | 0.63-1.08 | 1.01-1.26 | 1.03-1.27 | 1.01-1.53 |     |                  |
| Multivariable-adjusted HR |             | 0.92  | 1.14      | 1.17    | 1.32    | 1.32 | 0.001            |
| 95% CI<sup>b</sup> |                        | 0.69-1.23 | 1.01-1.29 | 1.04-1.31 | 1.06-1.65 |     |                  |
| Stomach, No.    |                         | 7     | 58        | 48      | 50      | 6   |                  |
| Age-adjusted HR |                         | 1.3   | 1.26      | 1.04    | 0.95    | 0.95 | 0.860            |
| 95% CI          |                         | 0.60-2.85 | 0.86-1.84 | 0.71-1.52 | 0.41-2.20 |     |                  |
| Multivariable-adjusted HR |           | 1.69  | 1.31      | 0.97    | 0.64    | 0.64 | 0.263            |
| 95% CI<sup>b</sup> |                        | 0.76-3.75 | 0.86-1.99 | 0.63-1.49 | 0.23-1.81 |     |                  |
| Colo rectal, No.|                         | 5     | 75        | 67      | 84      | 17  |                  |
| Age-adjusted HR |                         | 0.7   | 1.35      | 1.33    | 2.04    | 2.04 | 0.003            |
| 95% CI          |                         | 0.28-1.73 | 0.97-1.88 | 0.98-1.82 | 1.21-3.46 |     |                  |
| Multivariable-adjusted HR |           | 0.97  | 1.37      | 1.23    | 2.31    | 2.31 | 0.018            |
| 95% CI<sup>b</sup> |                        | 0.39-2.42 | 0.95-1.97 | 0.86-1.76 | 1.33-4.03 |     |                  |
| Liver, No.      |                         | 4     | 33        | 26      | 33      | 6   |                  |
| Age-adjusted HR |                         | 1.22  | 1.18      | 1.17    | 1.61    | 1.61 | 0.390            |
| 95% CI          |                         | 0.43-3.46 | 0.71-1.98 | 0.72-1.90 | 0.67-3.84 |     |                  |
| Multivariable-adjusted HR |           | 0.99  | 1.15      | 1.1     | 1.51    | 1.51 | 0.489            |
| 95% CI<sup>b</sup> |                        | 0.30-3.26 | 0.66-1.98 | 0.65-1.86 | 0.57-3.95 |     |                  |
| Pancreas, No.   |                         | 2     | 16        | 19      | 21      | 21  |                  |
| Age-adjusted HR |                         | 1.22  | 1.77      | 1.51    | 1.09    | 1.09 | 0.419            |
| 95% CI          |                         | 0.28-5.30 | 0.91-3.45 | 0.79-2.90 | 0.25-4.76 |     |                  |
| Multivariable-adjusted HR |           | 1.02  | 2.21      | 1.85    | 1.32    | 1.32 | 0.298            |
| 95% CI<sup>b</sup> |                        | 0.13-8.06 | 1.01-4.85 | 0.85-4.01 | 0.28-6.15 |     |                  |
| Lung, No.       |                         | 2     | 103       | 58      | 63      | 63  |                  |
| Age-adjusted HR |                         | 0.21  | 0.86      | 0.74    | 0.44    | 0.44 | 0.168            |
| 95% CI          |                         | 0.05-0.85 | 0.62-1.18 | 0.54-1.01 | 0.18-1.09 |     |                  |
| Multivariable-adjusted HR |           | 0.27  | 0.91      | 0.73    | 0.45    | 0.45 | 0.205            |
| 95% CI<sup>b</sup> |                        | 0.07-1.09 | 0.64-1.29 | 0.51-1.05 | 0.17-1.25 |     |                  |
| Breast, No.     |                         | 5     | 40        | 35      | 39      | 39  |                  |
| Age-adjusted HR |                         | 1.5   | 1.35      | 1.23    | 1.66    | 1.66 | 0.336            |
| 95% CI          |                         | 0.59-3.80 | 0.86-2.12 | 0.80-1.91 | 0.74-3.70 |     |                  |
| Multivariable-adjusted HR |           | 1.58  | 1.2       | 1.36    | 2.3     | 2.3  | 0.138            |
| 95% CI<sup>b</sup> |                        | 0.62-4.06 | 0.71-2.02 | 0.83-2.22 | 1.00-5.29 |     |                  |
| Uterine cervix, No.|                      | 0     | 17        | 7       | 20      | 20  |                  |
| Age-adjusted HR |                         | 0     | 1.63      | 1.43    | 1.08    | 1.08 | 0.161            |
| 95% CI          |                         | 0     | 0.26-1.51 | 0.75-2.73 | 0.25-4.69 |     |                  |
| Multivariable-adjusted HR |           | 0     | 0.53      | 1.41    | 0.67    | 0.67 | 0.328            |
| 95% CI<sup>b</sup> |                        | 0     | 0.19-1.47 | 0.68-2.94 | 0.09-5.15 |     |                  |
| Thyroid, No.    |                         | 14    | 255       | 185     | 235     | 235 |                  |
| Age-adjusted HR |                         | 0.69  | 1.12      | 1.18    | 1.46    | 1.46 | 0.003            |
| 95% CI          |                         | 0.40-1.19 | 0.93-1.36 | 0.99-1.41 | 1.04-2.04 |     |                  |

(Continues)
| Site of SPC | Prediagnosis BMI, kg/m² | <18.5 | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | \(P_{\text{trend}}\) |
|------------|-------------------------|-------|-----------|---------|---------|-----|------------------|
| Multivariable-adjusted HR | | 0.61 | 1 | 1.23 | 1.41 | 1.8 | <0.001 |
| 95% CI | | 0.34-1.09 | 0.99-1.53 | 1.15-1.73 | 1.24-2.61 |
| Lymphoma, No. | | 0 | 12 | 9 | 18 | 2 | |
| Age-adjusted HR | | 0 | 1 | 1.15 | 1.85 | 1.56 | 0.057 |
| 95% CI | | 0 | 0.48-2.72 | 0.89-3.85 | 0.35-6.99 |
| Multivariable-adjusted HR | | 0 | 1 | 1.05 | 1.64 | 1.8 | 0.103 |
| 95% CI | | 0 | 0.42-2.63 | 0.74-3.65 | 0.39-8.36 |
| Ovary, No. | | 1 | 15 | 7 | 17 | 3 | |
| Age-adjusted HR | | 0.79 | 1 | 0.72 | 1.42 | 1.87 | 0.169 |
| 95% CI | | 0.10-5.99 | 0.29-1.76 | 0.71-2.84 | 0.54-6.46 |
| Multivariable-adjusted HR | | 1.2 | 1 | 0.92 | 2.09 | 2.77 | 0.041 |
| 95% CI | | 0.15-9.41 | 0.33-2.55 | 0.93-4.70 | 0.73-10.43 |
| Oral cavity and pharynx/ | | 0 | 17 | 6 | 12 | 3 | |
| Esophagus/larynx, No. | | Age-adjusted HR | | 0 | 1 | 0.54 | 0.85 | 1.6 | 0.488 |
| 95% CI | | 0 | 0.21-1.36 | 0.41-1.78 | 0.47-5.45 |
| Multivariable-adjusted HR | | 0 | 1 | 0.47 | 0.75 | 1.86 | 0.552 |
| 95% CI | | 0 | 0.17-1.31 | 0.33-1.71 | 0.52-6.62 |
| Gallbladder and other biliary, | | 1 | 16 | 15 | 16 | 2 | |
| No. | | Age-adjusted HR | | 0.6 | 1 | 1.4 | 1.14 | 1.08 | 0.728 |
| 95% CI | | 0.08-4.54 | 0.69-2.83 | 0.57-2.29 | 0.25-4.71 |
| Multivariable-adjusted HR | | 0.95 | 1 | 1.36 | 1.3 | 1.31 | 0.538 |
| 95% CI | | 0.12-7.38 | 0.61-3.05 | 0.59-2.83 | 0.29-6.01 |
| Uterine corpus, No. | | 1 | 14 | 16 | 17 | 1 | |
| Age-adjusted HR | | 0.91 | 1 | 1.77 | 1.56 | 0.69 | 0.465 |
| 95% CI | | 0.12-6.91 | 0.86-3.62 | 0.77-3.16 | 0.09-5.23 |
| Multivariable-adjusted HR | | 0.88 | 1 | 1.77 | 2.09 | 1.19 | 0.134 |
| 95% CI | | 0.11-6.81 | 0.79-3.99 | 0.95-4.59 | 0.15-9.34 |
| Kidney, No. | | 1 | 8 | 15 | 11 | 2 | |
| Age-adjusted HR | | 1.36 | 1 | 2.85 | 1.67 | 2.29 | 0.279 |
| 95% CI | | 0.17-10.90 | 1.21-6.73 | 0.67-4.15 | 0.49-10.79 |
| Multivariable-adjusted HR | | 1.71 | 1 | 2.7 | 1.28 | 1.98 | 0.692 |
| 95% CI | | 0.21-13.98 | 1.08-6.74 | 0.47-3.52 | 0.40-9.84 |
| Urinary bladder, No. | | 1 | 11 | 6 | 5 | 0 | |
| Age-adjusted HR | | 0.88 | 1 | 0.82 | 0.52 | 0 | 0.136 |
| 95% CI | | 0.11-6.84 | 0.30-2.21 | 0.18-1.51 | 0- |
| Multivariable-adjusted HR | | 1.47 | 1 | 0.8 | 0.56 | 0 | 0.131 |
| 95% CI | | 0.18-11.95 | 0.26-2.46 | 0.18-1.77 | 0- |
| Leukemia, No. | | 1 | 13 | 7 | 7 | 1 | |
| Age-adjusted HR | | 0.89 | 1 | 0.82 | 0.67 | 0.72 | 0.447 |
| 95% CI | | 0.12-6.78 | 0.33-2.07 | 0.27-1.67 | 0.10-5.54 | (Continues) |
In obese women (BMI ≥ 25 kg/m²), the age-standardized IR of SPCs was approximately 2.5 times greater than that of the first primary cancers (577.31 vs 232.72 per 100 000 person-years; \( P < 0.001 \)). In addition, the age-standardized IR of obesity-related cancers was also higher for SPCs (67.37 per 100 000 person-years) than for first primary cancer (39.22 per 100 000 person-years; \( P < 0.001 \)) in the obese population.

### 3.3 Associations between prediagnosis BMI and SPCs

There were positive linear trends in the associations between prediagnosis BMI and overall risk of SPC, thyroid, colorectal, ovary, obesity-related, and obesity-related female cancers (\( P_{\text{trend}} < 0.05 \); Table 3). Compared with normal BMI patients, overweight cancer survivors had higher risk of overall SPC (aHR, 1.14; 95% CI, 1.01-1.29), pancreas (aHR, 2.21; 95% CI, 1.01-4.85), kidney (aHR, 2.70; 95% CI, 1.06-7.64), and obesity-related (aHR, 1.57; 95% CI, 1.16-2.14) cancers. Obese female cancer survivors had a higher risk of overall SPC (aHR, 1.17; 95% CI, 1.04-1.32) and thyroid cancer (aHR, 1.41; 95% CI, 1.15-1.73). In addition, severely obese cancer female survivors showed a higher risk of developing an overall SPC (aHR, 1.32; 95% CI, 1.06-1.65), colorectal (aHR, 2.31; 95% CI, 1.33-4.03), thyroid (aHR, 1.79; 95% CI, 1.24-2.61), and obesity-related (aHR, 2.03; 95% CI, 1.24-3.33) cancers. The risk of development of obesity-related female cancer as SPC also was higher in overweight and obese female cancer survivors (aHR for BMI 23.0-24.9 kg/m², 1.41; 95% CI, 1.09-1.82, aHR for BMI 25.0-29.9 kg/m², 1.35; 95% CI, 1.05-1.72, and aHR for BMI ≥ 30.0 kg/m², 2.10; 95% CI, 1.40-3.14, \( P_{\text{trend}} = 0.001 \)). When we computed \( P_{\text{heterogeneity}} \) for each type of SPC across the BMI categories, there were no statistically significant differences for the multivariable-adjusted hazard ratios for SPCs across the BMI categories in female cancer survivors.

The BMI-SPC risk association was statistically significant in female cancer survivors without smoking history (\( P_{\text{trend}} = 0.001 \)), with a localized stage in the first primary cancer (\( P_{\text{trend}} = 0.014 \)) and an obesity-related cancer as the first cancer (\( P_{\text{trend}} = 0.036 \), Table 4). In addition, the BMI-SPC risk association was higher among cancer survivors living in metropolitan areas (aHR for BMI ≥ 30.0 kg/m², 2.05; 95% CI, 1.22-3.46; \( P_{\text{trend}} = 0.001 \)).

In analyses of SPC risk that allowed for death as a competing risk, subdistribution HRs for SPC were statistically significant in overweight (aHR, 1.06; 95% CI, 1.03-1.29) and obese (aHR, 1.09; 95% CI, 1.06-1.12) female cancer survivors (\( P_{\text{trend}} < 0.001 \)). Five-year cumulative mortality among female cancer survivors was higher in the overweight (65.27%), obese (63.78%), and severely obese (62.90%) female cancer survivors than in the normal (66.50%) and underweight (54.87%) groups. Compared to groups with normal BMI, the severely obese survivors had a subdistribution HR for death of 1.13 (95% CI, 1.11-1.16; \( P_{\text{trend}} < 0.001 \)).

### TABLE 3 (Continued)

| Site of SPC | Prediagnosis BMI, kg/m² | <18.5 | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | \( P_{\text{trend}}^a \) |
|-------------|--------------------------|-------|-----------|---------|---------|-----|------------------|
| Multivariable-adjusted HR | 1.22 | 1 | 0.8 | 0.72 | 1 | 0.583 |
| 95% CI\(^b\) | 0.16-9.50 | 0.29-2.19 | 0.257-2.00 | 0.13-8.00 |
| Obesity-related, No.\(^c\) | 8 | 101 | 103 | 118 | 21 |
| Age-adjusted HR | 0.82 | 1 | 1.54 | 1.39 | 1.87 | 0.0014 |
| 95% CI | 0.40-1.69 | 1.17-2.03 | 1.06-1.81 | 1.17-2.99 |
| Multivariable-adjusted HR | 1.02 | 1 | 1.57 | 1.3 | 2.03 | 0.013 |
| 95% CI\(^b\) | 0.47-2.21 | 1.16-2.14 | 0.96-1.76 | 1.24-3.33 |
| Obesity-related female, No.\(^d\) | 14 | 156 | 154 | 174 | 31 |
| Age-adjusted HR | 0.97 | 1 | 1.41 | 1.35 | 1.81 | 0.001 |
| 95% CI | 0.56-1.68 | 1.13-1.77 | 1.09-1.67 | 1.23-2.67 |
| Multivariable-adjusted HR | 1.22 | 1 | 1.41 | 1.35 | 2.10 | 0.001 |
| 95% CI\(^b\) | 0.69-2.17 | 1.09-1.82 | 1.05-1.72 | 1.40-3.14 |

No. indicates the number of patients with SPC.

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SPC, secondary primary cancer.

\(^a\)Tests for trends were performed by assigning a median value for the BMI and treating the new variable as a continuous term in the models.

\(^b\)The multivariable hazard ratio model used Cox proportional analysis and adjusted age (continuous variable), smoking status, alcohol consumption frequency, physical activity times, fasting serum glucose level, fasting serum cholesterol level, comorbidity, and average insurance premium per month.

\(^c\)Includes colorectal, kidney, pancreatic, and esophageal cancers.

\(^d\)Includes colorectal, kidney, pancreatic, esophageal, breast, and urinary bladder cancers.

\( P < 0.001 \) (Table 2). In obese women (BMI ≥ 25 kg/m²), the age-standardized IR of SPCs was approximately 2.5 times greater than that of the first primary cancers (577.31 vs 232.72 per 100 000 person-years; \( P < 0.001 \)). In addition, the age-standardized IR of obesity-related cancers was also higher for SPCs (67.37 per 100 000 person-years) than for first primary cancer (39.22 per 100 000 person-years; \( P < 0.001 \)) in the obese population.
## TABLE 4  Stratified, multivariable analysis of risk of any SPC by prediagnosis BMI in female cancer survivors

| Prediagnosis BMI, kg/m² | <18.5 | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | \( P_{\text{trend}}^{a} \) |
|-------------------------|-------|-----------|----------|---------|-----|-----------------|
| **Smoking status**      |       |           |          |         |     |                 |
| Never-smoker, No.        | 53    | 696       | 524      | 681     | 99  |                 |
| Multivariable-adjusted HR | 0.99  | 1         | 1.14     | 1.19    | 1.36| 0.001           |
| 95% CI \( b \)    | 0.74-1.32 | 1.00-1.29 | 1.05-1.34 | 1.08-1.70 |
| Ever-smoker, No.         | 2     | 49        | 30       | 18      | 2   |                 |
| Multivariable-adjusted HR | 0.34  | 1         | 1.28     | 0.81    | 0.65| 0.976           |
| 95% CI \( b \)    | 0.08-1.41 | 0.77-2.15 | 0.45-1.44 | 0.16-2.76 |
| **Age at first cancer diagnosis** |       |           |          |         |     |                 |
| Age < 60 y, No.          | 30    | 470       | 272      | 338     | 47  |                 |
| Multivariable-adjusted HR | 0.95  | 1         | 1.00     | 1.12    | 1.18| 0.119           |
| 95% CI \( b \)    | 0.64-1.42 | 0.85-1.18 | 0.95-1.32 | 0.84-1.67 |
| Age ≥ 60 y, No.          | 26    | 302       | 299      | 381     | 57  |                 |
| Multivariable-adjusted HR | 1.10  | 1         | 1.19     | 1.103   | 1.29| 0.186           |
| 95% CI \( b \)    | 0.73-1.67 | 1.00-1.422 | 0.93-1.30 | 0.96-1.74 |
| **Stage**                |       |           |          |         |     |                 |
| Localized, No.           | 17    | 288       | 204      | 292     | 36  |                 |
| Multivariable-adjusted HR | 0.75  | 1         | 1.09     | 1.21    | 1.10| 0.014           |
| 95% CI \( b \)    | 0.47-1.19 | 0.91-1.30 | 1.03-1.43 | 0.77-1.56 |
| Regional, No.            | 16    | 134       | 119      | 124     | 18  |                 |
| Multivariable-adjusted HR | 1.71  | 1         | 1.494    | 1.22    | 1.54| 0.208           |
| 95% CI \( b \)    | 1.03-2.84 | 1.16-1.92 | 0.95-1.57 | 0.98-2.41 |
| Distance, No.            | 6     | 66        | 49       | 50      | 9   |                 |
| Multivariable-adjusted HR | 0.74  | 1         | 1.05     | 1.04    | 1.43| 0.681           |
| 95% CI \( b \)    | 0.30-1.83 | 0.72-1.54 | 0.72-1.51 | 0.70-2.92 |
| **Place of residence**   |       |           |          |         |     |                 |
| Metropolitan area, No.   | 11    | 110       | 123      | 133     | 18  |                 |
| Multivariable-adjusted HR | 1.33  | 1         | 1.76     | 1.63    | 2.05| 0.001           |
| 95% CI \( b \)    | 0.67-2.66 | 1.30-2.37 | 1.21-2.20 | 1.22-3.46 |
| City, No.                | 9     | 224       | 142      | 168     | 30  |                 |
| Multivariable-adjusted HR | 0.543 | 1         | 0.957    | 0.982   | 1.573| 0.167          |
| 95% CI \( b \)    | 0.27-1.10 | 0.76-1.21 | 0.78-1.23 | 1.05-2.37 |
| Rural county, No.        | 36    | 438       | 306      | 418     | 56  |                 |
| Multivariable-adjusted HR | 1.01  | 1         | 1.08     | 1.14    | 1.07| 0.126           |
| 95% CI \( b \)    | 0.71-1.44 | 0.92-1.27 | 0.98-1.33 | 0.78-1.46 |
| **Average insurance premium per month** |       |           |          |         |     |                 |
| 1st quarter, No.         | 12    | 160       | 135      | 159     | 26  |                 |
| Multivariable-adjusted HR | 0.90  | 1         | 1.27     | 1.2     | 1.46| 0.039           |
| 95% CI \( b \)    | 0.50-1.62 | 1.00-1.62 | 0.95-1.52 | 0.95-2.25 |
| 2nd quarter, No.         | 17    | 164       | 107      | 172     | 29  |                 |
| Multivariable-adjusted HR | 1.06  | 1         | 1.02     | 1.20    | 1.44| 0.060           |
| 95% CI \( b \)    | 0.63-1.77 | 0.79-1.31 | 0.95-1.51 | 0.95-2.19 |
| 3rd quarter, No.         | 11    | 175       | 122      | 134     | 16  |                 |

(Continues)
Comparison of the association between BMI and risk of first cancer in the general population

We compared the magnitude of the association between obesity and risk of SPC among female cancer survivors with the association between BMI and risk of first cancer in cancer-free general population (Table 5). We included 565,877 person-years of follow-up in our analysis, and we documented 146,377 patients with primary cancers. Overall, the BMI-cancer associations between BMI and first cancer risk were similar to associations between BMI and SPC risk in female cancer survivors. In the severely obese category, the aHRs for SPCs in female cancer survivors (aHR, 1.32; 95% CI, 1.06-1.65) were similar to those with first cancers in cancer-free general population (aHR, 1.20; 95% CI, 1.17-1.24, \( P_{\text{heterogeneity}} = 0.403 \)). In the obese category, the magnitude of the BMI-SPC risk association was similar to the association with the first cancers (aHR, 1.17; 95% CI, 1.04-1.31 vs aHR, 1.12; 95% CI, 1.10-1.13, \( P_{\text{heterogeneity}} = 0.461 \)).

| Prediagnosis BMI, kg/m² | <18.5 | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | \( P_{\text{trend}}^a \) |
|-------------------------|-------|-----------|---------|---------|-----|-----------------|
| Multivariable-adjusted HR | 0.80  | 1.09      | 0.97    | 0.92    | 0.963 |
| 95% CI\(^b\) | 0.43-1.47 | 0.85-1.39 | 0.76-1.24 | 0.55-1.56 |     |
| 4th quarter, No. | 13     | 170       | 123     | 168     | 22   |
| Multivariable-adjusted HR | 1.03  | 1.10      | 1.24    | 1.37    | 0.040 |
| 95% CI\(^b\) | 0.57-1.86 | 0.86-1.39 | 0.99-1.56 | 0.88-2.19 |     |

Presence of disability

| No disability, No. | 53     | 750       | 542     | 664     | 87   |
|---------------------|-------|-----------|---------|---------|-----|
| Multivariable-adjusted HR | 0.90  | 1.13      | 1.14    | 1.22    | 0.009 |
| 95% CI\(^b\) | 0.67-1.21 | 1.00-1.28 | 1.01-1.28 | 0.96-1.56 |     |
| Disability, No. | 3      | 22        | 29      | 55      | 17   |
| Multivariable-adjusted HR | 1.86  | 1.50      | 1.950   | 2.71    | 0.006 |
| 95% CI\(^b\) | 0.54-6.36 | 0.81-2.79 | 1.13-3.38 | 1.34-5.50 |     |

Cancer survivors whose first cancer was obesity-related cancer, No.\(^c\)

| Multivariable-adjusted HR | 1.33  | 1.36      | 1.34    | 1.57    | 0.036 |
| 95% CI\(^b\) | 0.71-2.49 | 1.03-1.79 | 1.03-1.74 | 0.97-2.54 |     |

Cancer survivors whose first cancer was obesity-related cancer, No.\(^d\)

| Multivariable-adjusted HR | 1.29  | 1.16      | 1.13    | 1.34    | 0.148 |
| 95% CI\(^b\) | 0.88-1.90 | 0.97-1.34 | 0.95-1.34 | 0.97-1.85 |     |

No. indicates the number of patients with SPC.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; SPC, secondary primary cancer.

\(^a\)Tests for trends were performed by assigning a median value for the BMI and treating the new variable as a continuous term in the models.
\(^b\)The multivariable hazard ratio model used Cox proportional analysis and adjusted age (continuous variable), smoking status, alcohol consumption frequency, physical activity times, fasting serum glucose level, fasting serum cholesterol level, comorbidity, and average insurance premium per month.
\(^c\)Includes colorectal, kidney, pancreatic, and esophageal cancers.
\(^d\)Includes colorectal, kidney, pancreatic, esophageal, breast, and endometrial cancers.

3.4 Comparison of the association between BMI and risk of first cancer in the general population

We compared the magnitude of the association between obesity and risk of SPC among female cancer survivors with the association between BMI and risk of first cancer in cancer-free general population (Table 5). We included 565,877 person-years of follow-up in our analysis, and we documented 146,377 patients with primary cancers. Overall, the BMI-cancer associations between BMI and first cancer risk were similar to associations between BMI and SPC risk in female cancer survivors. In the severely obese category, the aHRs for SPCs in female cancer survivors (aHR, 1.32; 95% CI, 1.06-1.65) were similar to those with first cancers in cancer-free general population (aHR, 1.20; 95% CI, 1.17-1.24, \( P_{\text{heterogeneity}} = 0.403 \)). In the obese category, the magnitude of the BMI-SPC risk association was similar to the association with the first cancers (aHR, 1.17; 95% CI, 1.04-1.31 vs aHR, 1.12; 95% CI, 1.10-1.13, \( P_{\text{heterogeneity}} = 0.461 \)).

4 DISCUSSION

Using the Korean female cancer survivor cohort, we demonstrated that obese female cancer survivors before first primary cancer diagnosis had a higher risk of subsequent SPC and increased risk of thyroid, colorectal, ovary, obesity-related, and obesity-related female cancers. In addition, the BMI-SPC risk association was statistically significant in female cancer survivors without smoking history, with a localized first primary cancer, and who lived in a metropolitan area. However, there was no difference in the magnitude of the association between obesity and SPC risk in female cancer survivors compared to that of primary cancer risk in cancer-free general population.

Previous studies reported that obesity is a risk factor for primary cancers, such as breast, colorectal, liver, and kidney in the general population,\(^{17-19,34}\) which is consistent with our finding that obesity increased the risk of first primary cancer. In this study, we could find the significant dose-dependent relationships between prediagnosis BMI.
### TABLE 5  HRs of first cancer by BMI in female cohort participants

| Site of first cancer | Prediagnosis BMI, kg/m² | <18.5 | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | \( P_{\text{trend}} \) |
|---------------------|-------------------------|-------|-----------|---------|---------|-----|-----------------|
| All, No.            | 4958                    | 54 277| 35 664    | 45 268  | 6 210   |     | <0.0001         |
| Age-adjusted HR     | 0.67                    | 1     | 1.34      | 1.46    | 1.55    |     |                 |
| 95% CI              | 0.65-0.69               | 1.32-1.35 | 1.44-1.48 | 1.51-1.59 |     |                 |
| Multivariable-adjusted HR | 0.83 | 1     | 1.08      | 1.12    | 1.20    |     | <0.0001         |
| 95% CI              | 0.81-0.86               | 1.06-1.09 | 1.10-1.13 | 1.17-1.24 |     |                 |
| Stomach, No.        | 853                     | 8781  | 5813      | 7297    | 909     |     |                 |
| Age-adjusted HR     | 0.707                   | 1     | 1.312     | 1.397   | 1.35    |     | <0.0001         |
| 95% CI              | 0.66-0.76               | 1.27-1.36 | 1.35-1.44 | 1.26-1.45 |     |                 |
| Multivariable-adjusted HR | 0.89 | 1     | 1.04      | 1.05    | 1.03    |     | <0.0001         |
| 95% CI              | 0.82-0.95               | 1.01-1.08 | 1.02-1.08 | 0.96-1.10 |     |                 |
| Colorectal, No.     | 596                     | 7569  | 5698      | 7694    | 1077    |     |                 |
| Age-adjusted HR     | 0.65                    | 1     | 1.49      | 1.77    | 2.09    |     | <0.0001         |
| 95% CI              | 0.57-0.74               | 1.40-1.58 | 1.67-1.86 | 1.89-2.31 |     |                 |
| Multivariable-adjusted HR | 0.72 | 1     | 1.24      | 1.41    | 1.77    |     | <0.0001         |
| 95% CI              | 0.63-0.83               | 1.17-1.32 | 1.33-1.49 | 1.59-1.96 |     |                 |
| Pancreas, No.       | 137                     | 1424  | 1154      | 1574    | 208     |     |                 |
| Age-adjusted HR     | 0.73                    | 1     | 1.48      | 1.63    | 1.67    |     | <0.0001         |
| 95% CI              | 0.61-0.86               | 1.37-1.60 | 1.52-1.75 | 1.44-1.93 |     |                 |
| Multivariable-adjusted HR | 0.82 | 1     | 1.20      | 1.25    | 1.28    |     | <0.0001         |
| 95% CI              | 0.69-0.98               | 1.11-1.30 | 1.16-1.35 | 1.10-1.48 |     |                 |
| Lung, No.           | 518                     | 4419  | 2862      | 3578    | 409     |     |                 |
| Age-adjusted HR     | 0.87                    | 1     | 1.214     | 1.245   | 1.11    |     | 0.002           |
| 95% CI              | 0.79-0.95               | 1.16-1.27 | 1.19-1.30 | 1.00-1.23 |     |                 |
| Multivariable-adjusted HR | 0.96 | 1     | 0.99      | 0.98    | 0.88    |     | 0.103           |
| 95% CI              | 0.88-1.06               | 0.95-1.04 | 0.93-1.02 | 0.80-0.98 |     |                 |
| Breast, No.         | 903                     | 12 943| 7254      | 8089    | 1160    |     |                 |
| Age-adjusted HR     | 0.50                    | 1     | 1.27      | 1.33    | 1.47    |     | <0.0001         |
| 95% CI              | 0.47-0.54               | 1.23-1.31 | 1.29-1.36 | 1.38-1.56 |     |                 |
| Multivariable-adjusted HR | 0.54 | 1     | 1.17      | 1.17    | 1.33    |     | <0.0001         |
| 95% CI              | 0.503-0.578             | 1.13-1.20 | 1.14-1.21 | 1.25-1.41 |     |                 |
| Uterine cervix, No. | 299                     | 2746  | 1589      | 2035    | 256     |     |                 |
| Age-adjusted HR     | 0.79                    | 1     | 1.24      | 1.42    | 1.38    |     | <0.0001         |
| 95% CI              | 0.71-0.89               | 1.17-1.32 | 1.34-1.51 | 1.21-1.57 |     |                 |
| Multivariable-adjusted HR | 0.93 | 1     | 1.07      | 1.16    | 1.11    |     | <0.0001         |
| 95% CI              | 0.83-1.06               | 1.00-1.14 | 1.09-1.24 | 0.97-1.27 |     |                 |
| Lymphoma, No.       | 140                     | 1458  | 955       | 1182    | 151     |     | 0.001           |
| Age-adjusted HR     | 0.71                    | 1     | 1.35      | 1.42    | 1.45    |     |                 |
| 95% CI              | 0.60-0.84               | 1.24-1.46 | 1.34-1.57 | 1.23-1.71 |     |                 |

(Continues)
| Site of first cancer | Prediagnosis BMI, kg/m² | 18.6-22.9 | 23-24.9 | 25-29.9 | ≥30 | \( P_{\text{trend}} \) |
|---------------------|------------------------|-----------|----------|---------|-----|-----------------|
| Multivariable-adjusted HR | 0.89 | 1 | 1.10 | 1.12 | 1.15 | 0.001 |
| 95% CI | 0.74-1.06 | | 1.01-1.20 | 1.03-1.22 | 0.97-1.37 | |
| Ovary, No. | 160 | 1551 | 1035 | 1196 | 171 | |
| Age-adjusted HR | 0.74 | 1 | 1.45 | 1.52 | 1.67 | <0.0001 |
| 95% CI | 0.63-0.87 | | 1.34-1.57 | 1.40-1.64 | 1.43-1.96 | |
| Multivariable-adjusted HR | 0.87 | 1 | 1.18 | 1.18 | 1.35 | <0.0001 |
| 95% CI | 0.74-1.03 | | 1.09-1.27 | 1.092-1.28 | 1.15-1.59 | |
| Oral cavity and pharynx/Esophagus/larynx, No. | 94 | 743 | 428 | 547 | 82 | |
| Age-adjusted HR | 0.92 | 1 | 1.16 | 1.27 | 1.48 | 0.536 |
| 95% CI | 0.75-1.14 | | 1.03-1.31 | 1.14-1.42 | 1.18-1.86 | |
| Multivariable-adjusted HR | 1.08 | 1 | 0.94 | 1.00 | 1.12 | 0.896 |
| 95% CI | 0.86-1.35 | | 0.83-1.07 | 0.89-1.13 | 0.88-1.42 | |
| Gallbladder and other biliary, No. | 144 | 1547 | 1235 | 1819 | 249 | |
| Age-adjusted HR | 0.70 | 1 | 1.46 | 1.74 | 1.86 | <0.0001 |
| 95% CI | 0.59-0.83 | | 1.36-1.58 | 1.63-1.87 | 1.63-2.13 | |
| Multivariable-adjusted HR | 0.78 | 1 | 1.18 | 1.36 | 1.48 | <0.0001 |
| 95% CI | 0.66-0.93 | | 1.09-1.27 | 1.26-1.46 | 1.29-1.70 | |
| Uterine corpus, No. | 77 | 1146 | 852 | 1225 | 287 | |
| Age-adjusted HR | 0.50 | 1 | 1.68 | 2.24 | 4.060 | <0.0001 |
| 95% CI | 0.40-0.62 | | 1.53-1.83 | 2.07-2.43 | 3.57-4.62 | |
| Multivariable-adjusted HR | 0.51 | 1 | 1.44 | 1.81 | 3.37 | <0.0001 |
| 95% CI | 0.40-0.65 | | 1.31-1.59 | 1.66-1.98 | 2.94-3.86 | |
| Kidney, No. | 61 | 740 | 566 | 826 | 121 | |
| Age-adjusted HR | 0.61 | 1 | 1.59 | 2.03 | 2.30 | <0.0001 |
| 95% CI | 0.48-0.79 | | 1.42-1.77 | 1.84-2.25 | 1.90-2.78 | |
| Multivariable-adjusted HR | 0.70 | 1 | 1.24 | 1.48 | 1.65 | <0.0001 |
| 95% CI | 0.52-0.93 | | 1.11-1.39 | 1.33-1.64 | 1.346-2.02 | |
| Urinary bladder, No. | 50 | 486 | 347 | 463 | 75 | |
| Age-adjusted HR | 0.76 | 1 | 1.30 | 1.40 | 1.75 | 0.001 |
| 95% CI | 0.57-1.01 | | 1.13-1.50 | 1.23-1.59 | 1.37-2.24 | |
| Multivariable-adjusted HR | 0.85 | 1 | 1.06 | 1.08 | 1.42 | 0.005 |
| 95% CI | 0.63-1.14 | | 0.92-1.22 | 0.95-1.24 | 1.10-1.82 | |
| Leukemia, No. | 109 | 806 | 523 | 619 | 87 | |
| Age-adjusted HR | 0.97 | 1 | 1.34 | 1.38 | 1.51 | 0.060 |
| 95% CI | 0.80-1.19 | | 1.20-1.49 | 1.24-1.54 | 1.21-1.88 | |
| Multivariable-adjusted HR | 1.14 | 1 | 1.15 | 1.18 | 1.26 | 0.009 |
| 95% CI | 0.93-1.40 | | 1.02-1.29 | 1.05-1.32 | 1.00-1.59 | |
| Others, No. | 582 | 5173 | 3308 | 4281 | 526 | |
| Age-adjusted HR | 0.82 | 1 | 1.23 | 1.33 | 1.27 | <0.0001 |
| 95% CI | 0.76-0.90 | | 1.18-1.29 | 1.28-1.39 | 1.16-1.38 | |

(Continues)
and overall SPCs including obesity-related, obesity-related female, and several individual SPCs. Previous studies have identified obese patients have experienced higher recurrences in colorectal, pancreatic, prostate, and breast cancers.35-38 In a cohort of over 10 000 breast cancer survivors, the HR of SPCs in overweight women was 2.23 (95% CI, 1.23-4.05) for endometrial cancer, 1.67 (95% CI, 0.99-2.82) for colorectal cancer, and 0.80 (95% CI, 0.28-2.99) for ovarian cancer.39 In a meta-analysis of prospective studies for excess body weight and SPC risk after breast cancer, obesity was associated with significantly increased risk of SPC of the contralateral breast (relative risk (RR), 1.37; 95% CI, 1.20-1.57), breast (RR, 1.40; 95% CI, 1.24-1.58), endometrium (RR, 1.96; 95% CI, 1.43-2.70), and colorectum (RR, 1.89; 95% CI, 1.28-2.79).23 In a pooled analysis of five prospective cohort studies for colorectal cancer survivors, overweight and obese survivors had an increased risk of a second obesity-associated cancer (aHR, 1.39; 95% CI, 1.01-1.92; aHR, 1.47; 95% CI, 1.02-2.12, respectively) compared to survivors with normal prediagnosis BMI.24 In a prospective cohort study of a large Korean population, the incidence of thyroid cancer was positively associated with higher BMI in women younger than 50 years of age (HR, 1.57 for BMI ≥ 25.0 Kg/m²; 95% CI, 1.28-1.92).40

The mechanisms by which obesity confers an increased risk of first primary cancer or SPCs are likely to be similar. The positive association between obesity and risk of SPC in female cancer survivors could be, in a large part, explained by increased circulating estrogen, other circulating hormones, or other growth factors, or by a low-grade chronic inflammatory state.21,41,42 Furthermore, it could be explained by additional genetic susceptibility or the carcinogenic effects due to cancer treatment. Interestingly, our study showed that higher BMI was more in female cancer survivors than in general population and the association between obesity and SPC risk among female cancer survivors was similar to that of first primary cancer risk in cancer-free general population. These findings are different from previous results that the strength of the BMI-cancer association was slightly stronger in male cancer survivors than in the general population.27 These suggest that association between obesity and risk of SPC could be different by gender. In addition, our study showed that the BMI-SPC risk association was statistically significant in female cancer survivors without smoking history and those with a localized first primary cancer. This suggests that obesity could affect SPC in female cancer survivors who have healthier lifestyle or expect longer life expectancy.

In subgroup analyses, the HR for SPC according to prediagnosis BMI was significantly higher in female cancer survivors who did not have smoking history or who had localized primary cancer. Smoking history would be a confounding factor in this study. In addition, it could be explained by that the cancer survivors have a relatively healthier lifestyle or because early-stage cancers might confer a greater chance for long-term survival, these findings could inform planning for long-term cancer survivorship programs, such as including early SPC detection.

Strengths of this study are that we could use the large-scaled, prospective cohort with approximate 150 000 female cancer survivors, including detailed information of prediagnosis behavioral risk factors. Our study design reduced recall bias, which could be a limitation in retrospective studies of cancer survivors. Specifically, height and weight, the main variables in our study, were measured by trained persons, not based on self-report. To our knowledge, this is the first large cohort study of female cancer survivors to show that prediagnosis BMI might affect the risk of the subsequent overall, obesity-related, and individual SPCs.

Because this is parallel study with the previous study for male cancer survivors,27 we have some limitations with the previous report. First, we could not consider the effects of cancer treatment on SPCs because of lack of detailed information about cancer treatment. This study has the possibility of selection bias because we analyzed only the population with height and weight data from the NHIS. This cohort has some possibility for SPC misclassification. Therefore, we performed sensitivity analyses for adjusting this possibility, excluding patients with SPC that diagnosed within 2 years after the first cancer diagnosis, and showed that the overall trends remained similar. In addition, we excluded thyroid cancer as primary cancer because thyroid cancer in Korea has been epidemiologically increased because of screening and

**TABLE 5** (Continued)

| Site of first cancer | Prediagnosis BMI, kg/m² | Multivariable-adjusted HR | 95% CI | P trend |
|---------------------|-------------------------|---------------------------|--------|--------|
|                     | <18.5                   | 18.6-22.9                 | 23-24.9 | 25-29.9 | ≥30    |
| Multivariable-adjusted HR | 1.00                  | 1                         | 1.01   | 1.04   | 1.02   | 0.093 |
| 95% CI               | 0.91-1.09               | 0.96-1.06                 | 1.00-1.09 | 0.93-1.12 |

No. indicates the number of patients with first cancer.

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

aTests for trends were performed by assigning a median value for the BMI and treating the new variable as a continuous term in the models.

bThe multivariable hazard ratio model used Cox proportional analysis and adjusted age (continuous variable), smoking status, alcohol consumption frequency, physical activity times, fasting serum glucose level, fasting serum cholesterol level, comorbidity, and average insurance premium per month.
considered as overdiagnosis. In this study, we could not evaluate the effect on the changes in BMI for female survivors because of the lack of data. So, we need to consider this limitation and try to perform the further study on the changes in BMI and SPC in future.

This study demonstrated that prediagnosis obesity increased risk of overall and individual SPCs in female cancer survivors. However, the magnitude of the association between obesity and SPC risk among female cancer survivors was similar to that of first primary cancer risk in the overall cohort. These findings suggest that lifestyle modification for weight reduction should be encouraged for prevention of primary cancer and SPCs, and individualized surveillance should be supported for obese female cancer survivors. In future, more studies should be performed to explain the different BMI-cancer associations by gender.

CONFLICT OF INTEREST
The authors have declared no conflicts of interest.

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