

# Development of second primary cancer in Korean breast cancer survivors

Hong Kyu Jung, Suyeon Park<sup>1</sup>, Nam Won Kim<sup>2</sup>, Jong Eun Lee<sup>3</sup>, Zisun Kim<sup>4</sup>, Sun Wook Han<sup>3</sup>, Sung Mo Hur<sup>4</sup>, Sung Young Kim<sup>3</sup>, Cheol Wan Lim<sup>4</sup>, Min Hyuk Lee<sup>2</sup>, Jihyoun Lee<sup>2</sup>

*Department of Surgery, Seran General Hospital, Seoul, <sup>1</sup>Department of Biostatistics, Soonchunhyang University Seoul Hospital, Seoul, <sup>2</sup>Department of Surgery, Soonchunhyang University Seoul Hospital, Seoul, <sup>3</sup>Department of Surgery, Soonchunhyang University Cheonan Hospital, Cheonan, <sup>4</sup>Department of Surgery, Soonchunhyang University Bucheon Hospital, Bucheon, Korea*

**Purpose:** Breast cancer survivors have slightly increased the risk of second primary cancers. Breast, colon, uterine, and ovarian cancers are common secondary cancers in breast cancer survivors. In this study, we assessed the development of second primary cancers of breast cancer survivors in Korea.

**Methods:** Medical records of patients with breast cancer in 3 tertiary medical institutions were reviewed retrospectively. We evaluated secondary malignancy diagnosed at least 2 months after the breast cancer diagnosis. Based on the International Classification of Disease-9 codes of malignancies, secondary primary breast cancer records were evaluated with person-year adjustment. The standardized incidence ratio (SIR) was assessed using national cancer incidence.

**Results:** A total of 3,444 treatment records were included from 3 medical centers. The cumulative incidence of overall second primary cancers was 2.8% (n = 93). The SIR was significantly higher in all sites (1.56; 95% confidence interval [CI], 1.26–1.91), endometrial cancer (5.65; 95% CI, 2.06–12.31), biliary tract cancer (3.96; 95% CI, 1.19–8.60), and thyroid cancer (2.29; 95% CI, 1.67–3.08).

**Conclusion:** The incidence of cancer was higher in breast cancer survivors compared to general population. Surveillance of secondary cancer in this group should be recommended individually considering the benefit related to the prognosis of primary breast cancer.

[Ann Surg Treat Res 2017;93(6):287-292]

**Key Words:** Breast neoplasms, Neoplasms, Second primary, Survivors, Early detection of cancer

## INTRODUCTION

Breast cancer is the second most common cancer in women in Korea. The incidence of female breast cancer observed in 2013 was more than twice compared to that in 1999, showing a sharp increase [1,2]. However, breast cancer survival has improved owing to the development of diagnostic and therapeutic techniques. In particular, the number of breast cancer survivors has increased up to 150-thousand women in Korea in 2013, and breast cancer accounts for almost one-fifth of all the prevalent cases of cancer in women. Therefore, there is a growing interest

in breast cancer survivor management, along with preventing secondary cancer.

Having a history of cancer can be associated to increased risk of cancer development [3]. Among the breast cancer survivors, the risk of developing contralateral breast cancer is higher than that of the general population. Carrying *BRCA1/2* gene mutation increases the risk of both ovarian and contralateral breast cancers. In addition to genetic factors, breast and endometrial cancers share other risk factors, such as low fertility, obesity, and hormone replacement therapy [4-7]. Treatment of breast cancer can be also associated with secondary malignancies. For

Received April 5, 2017, Revised May 15, 2017, Accepted May 23, 2017

Corresponding Author: Jihyoun Lee

Department of Surgery, Soonchunhyang University Seoul Hospital, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea

Tel: +82-2-709-9241, Fax: +82-2-710-3140

E-mail: lhthof@gmail.com

Copyright © 2017, the Korean Surgical Society

© Annals of Surgical Treatment and Research is an Open Access Journal. All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

example, it has been observed that tamoxifen increases the risk of endometrial cancer development [8], while radiation therapy may have been associated with the development of leukemia, endometrial and breast cancer [9].

In European studies, the incidence of uterine cancer, ovarian cancer, and soft tissue cancer was significantly increased in breast cancer survivors [10-12]. Another study conducted in an Asian population demonstrated higher incidence number of secondary cancer cases in cancer survivors than the expected incidence in the general population; significant increased secondary malignancies were ovarian cancer, thyroid cancer, and non-Hodgkin's lymphoma [13].

The incidence of malignancy depends on ethnic and environmental conditions. The development of secondary malignancies could be related to the incidence of common malignancy in that specific population. A single center study of Korean population reported nonsignificant difference in the relative risk of secondary cancers in breast cancer survivors. Endometrial, stomach, and thyroid cancer showed increased risk [14]. Therefore, in this study, we evaluated the relative risk of secondary cancers and its related factors.

## METHODS

Medical records of breast cancer patients, treated between January 1989 and May 2014 were collected from 3 tertiary medical centers in Korea, located at Seoul (center 1), Choeran (center 2), and Bucheon (center 3) city. We also searched the International Classification of Disease-9 codes of C00 to C97 except C50 that have been added after the initial diagnosis of breast cancer. Because there is no clear definition explaining the time interval of second primary cancer, we defined second primary cancer as the tumor diagnosed after 2 months from the initial diagnosis; otherwise, it was considered as a synchronous cancer [3]. Records from any visit within 1 year of the study period, as well as confirmed death records, were considered for the calculation of the person-years (PYs) number of each case. We excluded male breast cancer patients and patients aged under 20 years old, as well as patients with lack of follow-up data (without any visits within 2 months from the primary diagnosis or without treatment records). All the second primary cancer cases were thoroughly reviewed, and misleading information from breast cancer metastasis were excluded. We collected clinical data from medical records, including age at initial diagnosis, calendar year of breast cancer diagnosis, follow-up visit after primary diagnosis, time to develop second primary cancer, cause of death, and treatment of breast cancer. In particular, history of chemotherapy, radiation therapy, and endocrine treatment were evaluated.

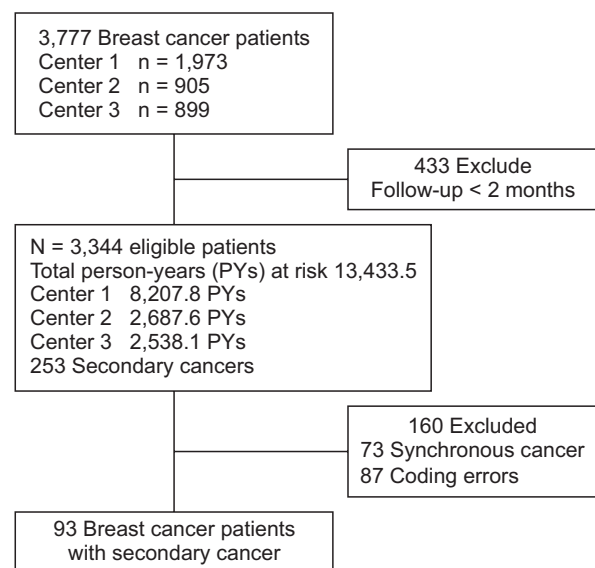
To compare the cancer risk of breast cancer survivor with that of the general population, Annual Report of Cancer Statistics

in Korea was used. Standardized incidence ratios (SIR) and 95% confidence intervals (CIs) were obtained by comparing observed and expected cancer incidence rates. SIRs were calculated by compiling PYs of observation from the date of breast cancer diagnosis to the date of death, date of diagnosis of a second cancer, or the last hospital visit. We calculated the estimated number of expected cases based on reference population (the Korean cancer annual incidence rate in 2012). A lower limit of 95% CI that was greater than 1.00 was considered to be statistically significant. Age subgroup was divided in 10-year interval, and the SIRs subgroups were calculated from the Korean age-specific cancer incidence rate.

Adjusted odd ratios were calculated with logistic regression analysis to analyze the relation between breast cancer treatment history and risk of second primary cancers. Analyses were conducted using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

## RESULTS

The medical records of 3,777 breast cancer patients were reviewed. After the exclusion of 433 patients, a total of 3,344 women were included in this study. The person-year at risk was 13,433.5 years. The median patient age at breast cancer diagnosis was 50 years (22–92 years). We reviewed 253 second primary cancer records and found 160 patients of those had synchronous cancer within 2 months after diagnosis, and 87 records were coding errors from metastatic lesions (Fig. 1). Among them, 93 patients (2.8%) were confirmed with second primary cancers. The overall SIR was 1.56 (95% CI, 1.26–1.91)



**Fig. 1.** Description of the study population. A total of 433 patients were excluded in the evaluation.

in breast cancer survivors compared to those of general population. The time to develop second primary cancer was 4.4 ± 3.95 years.

The most frequently observed second primary cancer was thyroid cancer (47.3%), followed by stomach cancer (10.8%)

**Table 1.** Secondary cancer after breast cancer diagnosis and standardized incidence ratio (SIR)

Cancer site	Observed case, n (%)	Expected case <sup>a)</sup>	SIR	95% CI
Esophagus	1 (1.1)	0.12	8.27	0.11–46.02
Stomach	10 (10.8)	5.35	1.87	0.90–3.44
Colon and rectum	4 (4.3)	6.17	0.65	0.17–1.66
Anus	1 (1.1)	0.08	12.41	0.16–69.03
Liver	2 (2.2)	2.19	0.91	0.10–3.30
Gallbladder and CBD	5 (5.4)	1.36	3.69	1.19–8.60
Lung	4 (4.3)	3.60	1.11	0.30–2.84
Cervix	4 (4.3)	1.91	2.10	0.56–5.37
Endometrium	6 (6.5)	1.06	5.65	2.06–12.31
Ovary	1 (1.1)	1.16	0.87	0.01–4.82
Kidney	1 (1.1)	0.08	12.41	0.16–69.03
Bladder	2 (2.2)	0.36	5.51	0.62–19.91
Thyroid	44 (47.3)	19.20	2.29	1.67–3.08
Hodgkin's lymphoma	1 (1.1)	0.04	24.81	0.32–138.06
Non-Hodgkin lymphoma	2 (2.2)	1.07	1.86	0.21–6.72
Acute myeloid leukemia	3 (3.2)	0.42	7.20	1.45–21.05
Skin	1 (1.1)	0.15	6.77	0.09–37.65
Muscle	1 (1.1)	0.23	4.38	0.06–24.36
Total	93 (100)	59.70	1.56	1.26–1.91

CI, confidence interval; CBD, common bile duct.  
<sup>a)</sup>Expected numbers following incident rate of general population.

and endometrial cancer (6.5%). Table 1 shows second primary cancers by site and their SIRs. Significantly increased SIRs were seen in endometrial cancer (5.65; 95% CI, 2.06–12.31), biliary tract cancers (3.96; 95% CI, 1.19–8.60), thyroid cancer (2.29; 95% CI, 1.67–3.08), and acute myeloid leukemia (AML) (7.20; 95% CI, 1.45–21.05). The SIR of lung cancer was 1.11 (95% CI, 0.30–2.84). Following the location of the medical center, secondary cancers observed in center 1 showed significantly elevated SIR in endometrial cancer (9.25) and thyroid cancer (2.73). Stomach cancer (3.74) was common in center 2.

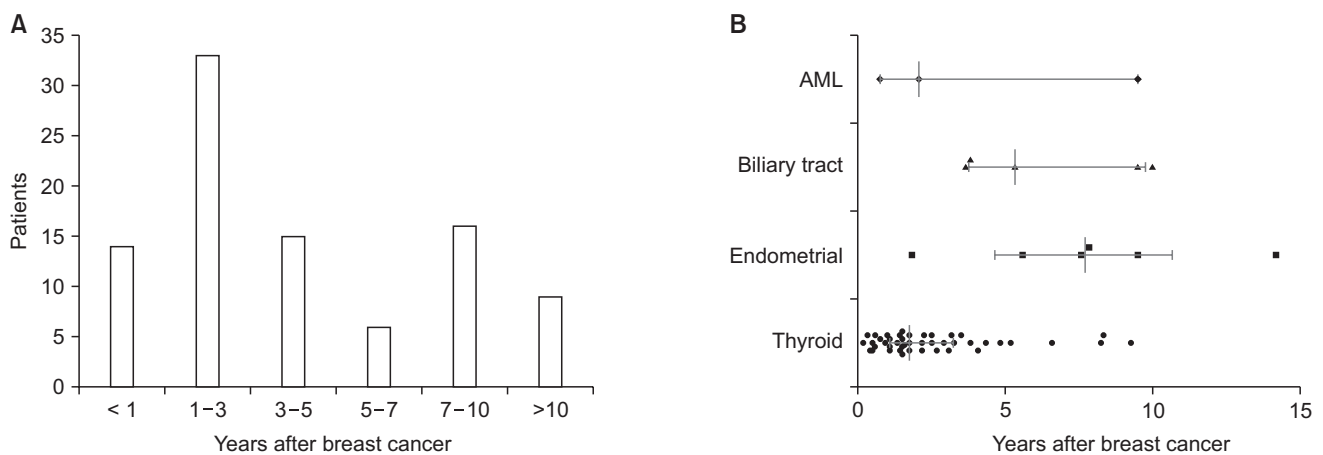
The number of secondary cancers was the highest in patients in the 50's, followed by those in the 40's and 60's. The SIRs according to age group are presented at Table 2. The age group of 30 to 39 years showed statistically significant SIR (2.59; 95% CI, 1.48–4.20). The secondary cancers were most frequently found 1–3 years after breast cancer diagnosis (Fig. 2A). Secondary cancer diagnosis after primary diagnosis of thyroid cancer, endometrial cancer, biliary tract cancer, and AML are presented in Fig. 2B.

We analyzed the incidence of second primary cancer

**Table 2.** Secondary cancers following the age at breast cancer diagnosis

Age group (yr)	Observed case	Expected case <sup>a)</sup>	SIR (95% CI)
30–39	16	6.18	2.59 (1.48–4.20)
40–49	28	25.54	1.10 (0.73–1.58)
50–59	35	27.14	1.29 (0.90–1.79)
60–69	18	16.22	1.11 (0.66–1.75)
≥70	8	10.12	0.79 (0.34–1.56)

SIR, standardized incidence ratio; CI, confidence interval.  
<sup>a)</sup>Expected numbers following incident rate of general population.



**Fig. 2.** Time to development of second primary cancer. Panel A presents the number of patients who were diagnosed with secondary cancer following the initial diagnosis. The first peak is observed from 1 to 3 years after primary cancer, and the second peak is seen from 7 to 10 years after primary cancer. Panel B shows the time interval of secondary cancers with significant SIR after primary cancer. AML, acute myeloid leukemia.

**Table 3.** History of adjuvant treatment of breast cancer and development of secondary cancers

Cancer site	Adjusted <sup>a)</sup> OR (95% CI)		
	Chemotherapy	Endocrine treatment	Radiotherapy
Stomach	0.15 (0.04–0.61)	0.82 (0.19–3.52)	0.49 (0.11–2.18)
Colon	NA	0.37 (0.05–2.90)	0.36 (0.04–3.71)
Liver	0.41 (0.02–6.92)	1.28 (0.08–21.48)	NA
Gallbladder and CBD	NA	NA	1.95 (0.30–12.80)
Lung	NA	NA	1.11 (0.06–20.49)
Cervix	NA	1.22 (0.12–12.64)	0.38 (0.04–3.80)
Endometrium	NA	0.83 (0.14–4.96)	2.54 (0.43–14.87)
Thyroid	0.61 (0.22–1.64)	0.63 (0.25–1.54)	1.81 (0.78–4.18)
Acute myeloid leukemia	0.46 (0.04–5.62)	NA	0.52 (0.04–6.16)

OR, odds ratio; CI, confidence interval; NA, not available; CBD, common bile duct.

<sup>a)</sup>P-value by logistic regression analysis.

according to the adjuvant treatment, including chemotherapy, endocrine treatment, and radiation therapy. The most frequent incidence of second primary cancer was thyroid cancer in all treatment groups. However, most of the treatment modalities showed no significant correlation between the treatment method and the development of carcinoma (Table 3).

## DISCUSSION

The incidence of secondary primary cancer observed in this study was higher in breast cancer survivors than in the general population. Significantly increased secondary cancers were thyroid cancer, endometrial cancer, bile duct cancer, and AML.

We found that thyroid cancer and gastric cancer were frequently observed after primary cancer, which is consistent with a previous study conducted in the Korean population [14]. Gastric cancer is a common malignancy in Korea; therefore, it might be influenced by the high number of observed cases in breast cancer survivors. In the same context, gastric cancer was also commonly seen in breast cancer survivors in Japan. Secondary thyroid cancer was commonly reported in many other countries [11,15,16], such as the United States, Japan, Canada, and Europe. A meta-analysis showed elevated risk of thyroid cancer in breast cancer patients and elevated risk of breast cancer in thyroid cancer patients was seen [17]. However, their association is still controversial, and there is lack of definite mechanisms of the association.

Adjuvant treatment of breast cancer has been considered a risk factor of secondary malignancy. Cytotoxic chemotherapy can induce therapy-related myeloid neoplasm, such as AML and myelodysplastic syndrome (MDS). In this study, we found 3 patients with AML (3.2% of the breast cancer survivors) and 2 of them had received cytotoxic chemotherapy. Specifically, one patient had received cyclophosphamide, methotrexate, and fluorouracil, while the other patient had received doxorubicin

and cyclophosphamide followed by docetaxel. Alkylating agents (cyclophosphamide, carboplatin, and cisplatin), topoisomerase II inhibitors (doxorubicin and epirubicin), and antitubulin agents (paclitaxel and docetaxel) are commonly used drugs in breast cancer treatment, but exposure to those drugs can be associated with AML and MDS occurrence. In a population-based study in the United States, the risk of AML in the cancer treatment group was 4.70 times higher than that in the general population. In breast cancer patients, the SIR was 4.60 and it was significant within the first 5 years (8.60) and 5 to 10 years (2.70) [18]. Although the number of patients was too small to draw statistical conclusions, 2 patients were treated with chemotherapy as they had been diagnosed with AML 10 years after breast cancer diagnosis (Fig. 2).

The relationship between tamoxifen treatment and risk of endometrial cancer has been reported in many studies [19,20], while the incidence was low in patients treated with aromatase inhibitors [21]. In this study, an elevated risk of endometrial tumors in the endocrine treatment group was not observed, not only because of the small study population, but also because the effect of treatment drug, treatment duration, patient's adherence, and other risk factors for endometrial cancer, such as body mass index, were not assessed. Another example of treatment-related cancer is lung cancer caused after radiation treatment.

We found a significant relationship between the young age group and the risk of secondary malignancy, which is consistent with previous studies. Survivors who develop breast cancer at a young age might have more genetic and environmental risk factors, and aggressive treatment for breast cancer might lead to carcinogenesis [9,22,23]. Thus, further attention might be required in the young population. Currently, the surveillance of breast cancer survivors after initial treatment is recommended following their symptoms [24], and there are no evident guidelines for tailored surveillance of secondary malignancies

for breast cancer survivors.

The risk of secondary cancers can differ between individuals depending on the administered adjuvant treatment and their basic risks. We observed an increased risk of thyroid cancer, endometrial cancer, bile duct cancer, and AML in Korean breast cancer survivors. It is difficult to distinguish between metastatic lesions and second primary malignancy in some organs, such as the biliary tract, pancreas, lungs, or ovaries.

We found increased risk of second primary cancer in breast cancer survivors. Although there was a significant difference in biliary tract cancer development in this study, however, it cannot be directly concluded that all patients should receive surveillance of those cancers because this study has limitation that it was a retrospective study and there were small population of secondary cancers. Consideration of patient's life

expectancy from the primary tumor and these increased risks might be important for secondary cancer surveillance in breast cancer survivors.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGEMENTS

The present research has been supported by Korea Breast Cancer Foundation and the Soonchunhyang University Research Fund.

## REFERENCES

- Oh CM, Won YJ, Jung KW, Kong HJ, Cho H, Lee JK, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2013. *Cancer Res Treat* 2016; 48:436-50.
- National Cancer Center. Annual report of cancer statistics in Korea in 2012. Goyang (Korea): National Cancer Center; 2014.
- Curtis RE, Freedman DM, Ron E, Ries LA, Hacker DG, Edwards BK, editors. New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000. National Cancer Institute. NIH Publ. No. 05-5302. Bethesda (MD): National Cancer Institute; 2006.
- Hulka BS, Brinton LA. Hormones and breast and endometrial cancers: preventive strategies and future research. *Environ Health Perspect* 1995;103 Suppl 8: 185-9.
- La Vecchia C, Brinton LA, McTiernan A. Cancer risk in menopausal women. *Best Pract Res Clin Obstet Gynaecol* 2002;16: 293-307.
- Brinton LA, Moghissi KS, Scoccia B, Westhoff CL, Lamb EJ. Ovulation induction and cancer risk. *Fertil Steril* 2005;83: 261-74.
- Druesne-Pecollo N, Touvier M, Barrandon E, Chan DS, Norat T, Zelek L, et al. Excess body weight and second primary cancer risk after breast cancer: a systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat* 2012;135: 647-54.
- Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med* 2003; 18:937-47.
- Yu GP, Schantz SP, Neugut AI, Zhang ZF. Incidences and trends of second cancers in female breast cancer patients: a fixed inception cohort-based analysis (United States). *Cancer Causes Control* 2006;17: 411-20.
- Andersson M, Jensen MB, Engholm G, Henrik Storm H. Risk of second primary cancer among patients with early operable breast cancer registered or randomised in Danish Breast Cancer cooperative Group (DBCG) protocols of the 77, 82 and 89 programmes during 1977-2001. *Acta Oncol* 2008;47:755-64.
- Mellemkjaer L, Friis S, Olsen JH, Scelo G, Hemminki K, Tracey E, et al. Risk of second cancer among women with breast cancer. *Int J Cancer* 2006;118:2285-92.
- Volk N, Pompe-Kirn V. Second primary cancers in breast cancer patients in Slovenia. *Cancer Causes Control* 1997;8:764-70.
- Tanaka H, Tsukuma H, Koyama H, Kinoshita Y, Kinoshita N, Oshima A. Second primary cancers following breast cancer in the Japanese female population. *Jpn J Cancer Res* 2001;92:1-8.
- Kim JY, Song HS. Metachronous double primary cancer after treatment of breast cancer. *Cancer Res Treat* 2015;47:64-71.
- Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. *Br J Cancer* 2006;94: 1745-50.
- Kamigaki Y, Kawakami K. Risk of second cancer after initial treatment of breast cancer: an Osaka Cancer Registry Database study. *Oncol Lett* 2011;2:963-73.
- Joseph KR, Edirimanne S, Eslick GD. The association between breast cancer and thyroid cancer: a meta-analysis. *Breast Cancer Res Treat* 2015;152:173-81.
- Morton LM, Dores GM, Tucker MA, Kim CJ, Onel K, Gilbert ES, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. *Blood* 2013;121:2996-3004.
- Peters-Engl C, Frank W, Danmayr E, Friedl HP, Leodolter S, Medl M. Association bet-

- ween endometrial cancer and tamoxifen treatment of breast cancer. *Breast Cancer Res Treat* 1999;54:255-60.
20. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994;86:527-37.
21. Chlebowski RT, Schottinger JE, Shi J, Chung J, Haque R. Aromatase inhibitors, tamoxifen, and endometrial cancer in breast cancer survivors. *Cancer* 2015;121:2147-55.
22. Brown LM, Chen BE, Pfeiffer RM, Schairer C, Hall P, Storm H, et al. Risk of second non-hematological malignancies among 376,825 breast cancer survivors. *Breast Cancer Res Treat* 2007;106:439-51.
23. Molina-Montes E, Requena M, Ssnchez-Cantalejo E, Fernandez MF, Arroyo-Morales M, Espin J, et al. Risk of second cancers cancer after a first primary breast cancer: a systematic review and meta-analysis. *Gynecol Oncol* 2015;136:158-71.
24. Wilbur J. Surveillance of the adult cancer survivor. *Am Fam Physician* 2015;91:29-36.