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Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972–2001

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Abstract

A cohort of 9919 breast cancer patients from the population-based Eindhoven Cancer Registry was followed for vital status and development of second cancer. Person-year analysis was applied to determine the risk of second primary breast or urogenital cancer among breast cancer patients and to assess its correlation with age, treatment and time since the first breast cancer diagnosis. Women with previous breast cancer have an elevated risk of overall second breast or urogenital cancer. The largest relative risk was observed for second breast cancer (SIR (standardised incidence ratio) 3.5; 95% confidence interval (CI) 3.2–3.8) and second ovarian cancer (SIR 1.7; 95% CI 1.2–2.3). The absolute excess risk was highest for second breast cancer (64/10,000 patients/year). However, breast cancer has an inverse relationship to risk of cervical cancer. Changes in behavioural risk factors are important for lowering the risk of second cancer after breast cancer.

Keywords: Breast cancer; Long term; Second primary breast or urogenital cancer; Treatment

1. Introduction

A history of breast cancer is a risk indicator for second primary cancer among women, especially for second primary breast and genital cancer. Higher risks have been found of second breast cancer [1,2], subsequent ovarian cancer [2] and uterine cancer [3,4] after primary breast cancer [5]. However, the association with cervical cancer and cancer of the vagina-vulva has not been studied in detail [2]. Only a few studies have shown an increased risk of second primary kidney and bladder cancer among breast cancer patients [6,7].

Examination of the association between breast cancer and second primary cancer may contribute to the development of preventive interventions. Understanding these issues may also help identify the treatment that carries the lowest risk of second cancer for breast cancer patients. In addition, it may also contribute to early detection of second cancer. Common risk factors, such as dietary habits, reproductive characteristics, exposure to exogenous oestrogen and genetic factors play an important role in the aetiology of second female cancers, particularly breast, uterine and ovarian cancer [8]. Breast cancer treatments, such as radiotherapy, systemic chemotherapy [6,9] and hormonal therapy, may be associated with a higher risk of certain second primary cancers among breast cancer patients. In addition, hormonal therapy with tamoxifen has been found to in-

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crease the risk of cancer of the uterus, in particular mixed mullerian tumours [10–12].

The effect of factors such as latency time, cancer treatment and age at diagnosis on the risk of second female cancer remains unknown. Our cohort comprises the most recent data, with a long follow-up time and a large number of cases. This enables us to assess the role of important risk factors in the development of second primary cancer. The aim of this population-based cohort study was to determine the incidence of second primary breast and urogenital cancers among breast cancer patients in the south of The Netherlands, compared with the incidence expected in the general population, and to relate this incidence to the initial breast cancer treatment, follow-up time and age at breast cancer diagnosis.

2. Patients and methods

2.1. Patients

Breast cancer patients were selected from the Eindhoven Cancer Registry in the south of The Netherlands. This is a population-based cancer registry, which covered almost 2.3 million individuals in 2004. A detailed description of the data collection has been reported elsewhere [13].

We excluded patients with less than 1 year of follow-up time ($n = 1458$), patients with *in situ* primary breast cancer ($n = 458$), patients with other malignancies diagnosed before breast cancer, as well as patients with a second cancer that appeared to be a metastasis ($n = 44$). For the calculation of risks of second ovarian cancer, patients who were oophorectomised as treatment for breast cancer were not included in the analyses ($n = 9$). As a result, for the period 1972–2000, 9919 breast cancer patients older than 25 years were available for analysis.

Analyses were stratified according to age at diagnosis of the initial tumour (categories: pre-menopause (age <50 years) and post-menopause (age $\geqslant$50) years); initial treatment combination of breast cancer (categories: surgery (S), radiotherapy ± S, chemotherapy ± S, hormonal therapy ± S, radiotherapy and chemotherapy ± S, radiotherapy and hormonal therapy ± S); and other treatments (chemotherapy and hormonal therapy ± S, radio- and chemo- and hormonal therapy ± S, no treatment and unknown treatment); and follow-up time after diagnosis (categories: 1–4 years, 5–9 years, 10–14 years and longer than 15 years).

2.2. Methods

The risk of developing a second cancer was investigated by means of person-years analysis, corrected for age and calendar-year period to the date of death, date of last follow-up, date of diagnosis of the second cancer or end of the study (31st December 2001), whichever came first [14]. We compared the incidence of second primary tumours among patients with a diagnosis of breast cancer (the observed incidence) with the incidence for the same tumours in the general population (the expected incidence), which is expressed as the standardised incidence ratio (SIR). Calculation of the expected subsequent primary cancer was derived from the same population, using EUROCIM 4.2. The statistical significance and 95% confidence intervals (CI) were determined by means of exact Poisson probability [15]. The absolute excess risk (AER) was calculated by subtracting the expected number from the observed number and then dividing the difference by person-years at risk (per 10,000 breast cancer patients/year) [8]. All statistical analyses were performed using SPSS 11.5 for Windows (Statistical Products and Service Solution, Inc., Chicago, USA).

3. Results

Our cohort yielded 65,950 person-years. General characteristics at the time of primary breast cancer diagnosis are shown in Table 1. The average age at breast cancer diagnosis was 58.8 years, the average follow-up time was 6.6 years, and the median follow-up time was 4.9 years. Overall, 725 breast cancer patients developed second breast and urogenital cancer, compared with the expected 266 patients in the population (SIR 2.7; 95% CI 2.5–2.9) (Table 2). The relative risk of developing sec-

Table 1
Characteristics at diagnosis of first primary female breast cancer patients, diagnosed in the south of The Netherlands, 1972–2000

Characteristics	Number (%)	Second cancer (% of first primaries)
Period of diagnosis of first primary		
1972–1981	2676 (27.0)	267 (10.0)
1982–1991	3590 (36.2)	273 (7.6)
1992–2000	3653 (36.8)	185 (5.1)
Age at diagnosis		
<50 years	2950 (29.7)	295 (10.0)
$\geqslant$50 years	6969 (70.3)	430 (6.2)
Treatment combination		
Surgery (S)	2163 (21.8)	181 (8.4)
Radiotherapy ± S	4534 (45.7)	398 (8.8)
Chemotherapy ± S	301 (3.0)	12 (4.0)
Hormonal therapy ± S	609 (6.1)	21 (3.5)
Radio- and chemotherapy ± S	865 (8.7)	52 (3.4)
Radio- and hormonal therapy ± S	1214 (12.2)	48 (4.0)
Others	233 (2.3)	13 (5.6)
Follow-up period (years)		
1–4	5004 (50.4)	367 (7.3)
5–9	2758 (27.8)	205 (7.4)
10–14	1215 (12.2)	79 (6.5)
$\geqslant$15	942 (9.5)	74 (6.4)
Total	9919	725 (7.9)

Table 2
Observed (Obs.) and expected (Exp.) numbers of second primary female urogenital and breast cancers diagnosed in 1972–2001 and standardised incident ratio (SIR) with 95% confidence interval (CI) for breast cancer patients in the south of The Netherlands, diagnosed 1972–2000

Site of second cancer	Obs.	Exp.	SIR	CI	AER
All second cancer	725	265.9	2.7[a]	2.5–2.9	69.6
Female urogenital	137	70.4	1.9[a]	1.6–2.3	10.1
Breast	588	167.6	3.5[a]	3.2–3.8	63.7
Female genital tract					
Cervix uteri	9	9.8	0.9	0.4–1.8	−0.1
Corpus uteri	40	31.1	1.3	0.9–1.8	1.4
Ovarium	43	25.2	1.7[a]	1.2–2.3	2.7
Vagina-vulva	6	4.2	1.4	0.5–3.2	0.3
Female urinary tract					
Kidney	17	13.8	1.2	0.7–2.0	0.5
Bladder	22	16.7	1.3	0.8–2.0	0.8

AER, absolute excess risk/10,000 patients/year.
[a] 95% CI excludes 1.

ond urogenital cancer after excluding all second breast cancers was higher among breast cancer patients than in the general population (SIR 1.9; 95% CI 1.6–2.3). Markedly increased risks of second breast cancer (SIR 3.5; 95% CI 3.2–3.8) and ovarian cancer (SIR 1.7; 95% CI 1.2–2.3) were also observed among these patients. The absolute excess risk (AER) was highest for second breast cancer (64/10,000 person-years).

3.1. Age

In general, the increased overall risk of second urogenital cancer (SIR 2.1; 95% CI 1.9–2.3), second breast cancer (SIR 2.6; 95% CI 2.4–2.9) and second ovarian cancer (SIR 1.1; 95% CI 0.7–1.7) was more marked among patients who were diagnosed with breast cancer before menopause (Table 3). In contrast, no differences in the SIR were observed between patients diagnosed before and after menopause for second uterine, cervix, vagina-vulva, kidney and bladder cancer. A higher incidence ratio and absolute excess of second breast and ovarian cancer were observed among women diagnosed before menopause.

3.2. Treatment

The risk of second breast cancer was elevated regardless of type of initial treatment given for the first primary breast cancer. Treatment was not associated with the elevated risks of cervix, endometrial, vagina-vulva, kidney or bladder cancer compared with patients treated surgically (Table 4).

Furthermore, we assessed whether the excess risk of second breast and endometrial cancer among women aged 50 years and older receiving hormonal treatment ± radiotherapy was higher than the excess risk among women undergoing surgical treatment (data are not shown). We observed a significantly lower SIR for second breast cancer among women who received hormonal treatment ± radiotherapy (SIR 1.6 95% CI 1.2–2.2) than those who were treated surgically (SIR 2.8; 95% CI 2.3–3.4). In contrast, we observed a higher SIR for second endometrial cancer (SIR 1.7; 95% CI 0.7–3.4) among patients receiving hormonal treatment ± radiotherapy than among those undergoing surgical therapy (SIR 0.7 95% CI 0.2–1.8).

3.3. Follow-up time

The SIR for second breast cancer was 4.6 (95% CI 4.0–5.1) during the first 4 years of follow-up then it decreased steadily to 14 years of follow-up and then increased again after 15 years (SIR 4.7; 95% CI 3.5–

Table 3
Observed (Obs.) and expected (Exp.) numbers of second primary urogenital and breast cancers diagnosed in 1972–2001, standardised incident ratio (SIR) and absolute excess risk (AER) among breast cancer patients according to age at breast cancer diagnosis in the south of The Netherlands, diagnosed 1972–2000

Site of second cancer	Pre-menopausal primary				Post-menopausal primary			
	Person-years: 22,550				Person-years: 43,400			
	Obs.	Exp.	SIR	AER	Obs.	Exp.	SIR	AER
All second cancer	295	58.2	5.1[a]	105.0	430	207.7	2.1[a]	51.2
Female urogenital	40	14.5	2.7[a]	11.3	97	55.8	1.7[a]	9.5
Breast	255	40.8	6.3[a]	95.0	333	126.8	2.6[a]	47.5
Female genital tract								
Cervix uteri	5	2.9	1.7	0.9	4	6.9	0.6	−0.7
Corpus uteri	8	5.7	1.4	1.0	32	25.3	1.3	1.5
Ovarium	21	5.5	3.8[a]	6.9	22	19.8	1.1	0.5
Vagina-vulva	1	0.5	2.2	0.2	5	3.8	1.3	0.3
Female urinary tract								
Kidney	2	1.8	1.1	0.09	15	12.0	1.2	0.7
Bladder	3	1.8	1.7	0.5	19	14.9	1.3	0.9

AER, absolute excess risk/10,000 patients/year.
[a] 95% CI excludes 1.

Table 4
Observed (Obs.) and expected (Exp.) numbers of second primary urogenital cancers diagnosed in 1972–2001 and standardised incident ratio (SIR) according to breast cancer treatment for patients diagnosed with breast cancer in the south of The Netherlands in 1972–2000

Site of second cancer	Surgical			Radiotherapy[a]			Chemotherapy[b]			Hormonal therapy[c]			Radio- + chemotherapy[d]			Radio- + hormonal therapy[e]			Others[f]		
	Person-years: 17,323			Person-years: 33,444			Person-years: 1676			Person-years: 2489			Person-years: 4590			Person-years: 5611			Person-years: 817		
	Obs.	Exp.	SIR	Obs.	Exp.	SIR	Obs.	Exp.	SIR	Obs.	Exp.	SIR	Obs.	Exp.	SIR	Obs.	Exp.	SIR	Obs.	Exp.	SIR
All cancer	181	72.5	2.5[g]	398	132.6	3.0[g]	12	5.1	3.5[g]	21	11.5	1.8[g]	52	12.7	4.1[g]	48	27.3	1.8[g]	13	2.8	4.6[g]
Female urogenital	29	19.1	1.5	71	35.5	2.0[g]	4	1.3	3.1	3	3.2	0.9	8	3.2	2.5[g]	21	7.3	2.9[g]	1	0.7	1.4
Breast	152	45.1	3.4[g]	327	83.5	3.9[g]	8	3.5	2.3	18	8.0	2.3[g]	44	8.8	5.0[g]	27	17.0	1.6[g]	12	1.9	6.3[g]
Female genital																					
Cervix uteri	2	2.7	0.8	6	5.0	1.2	0	0.2	0	0	0.4	0	1	0.6	1.6	0	0.8	0	0	0.1	0
Corpus uteri	7	8.4	0.8	20	15.7	1.3	1	0.6	1.8	1	1.4	0.7	3	1.3	2.3	8	3.5	2.3	0	0.3	0
Ovarium	13	6.8	1.9	22	12.9	1.7[g]	2	0.5	4.2	0	1.1	0	2	1.2	1.7	3	2.6	1.1	1	0.3	4.0
Vagina-vulva	2	1.3	1.5	1	2.0	0.5	0	0.1	0	1	0.3	3.5	1	0.1	8.4	1	0.4	2.4	0	0.0	0
Female urinary																					
Kidney	1	4.0	0.3	10	6.9	1.5	1	0.2	5.1	0	0.7	0	0	0.4	0	5	1.5	3.3[g]	0	0.1	0
Bladder	4	4.9	0.8	12	8.1	1.5	0	0.2	0	1	1.1	0.9	1	0.5	2.2	4	1.9	2.2	0	0.2	0

[a] Radiotherapy ± S.
[b] Chemotherapy ± S.
[c] Hormonal therapy ± S.
[d] Radiotherapy and chemotherapy ± S.
[e] Radiotherapy and hormonal therapy ± S.
[f] Chemotherapy and hormonal therapy ± S, radio- and chemo- and hormonal therapy ± S, no treatment and unknown treatment.
[g] 95% CI excludes 1.

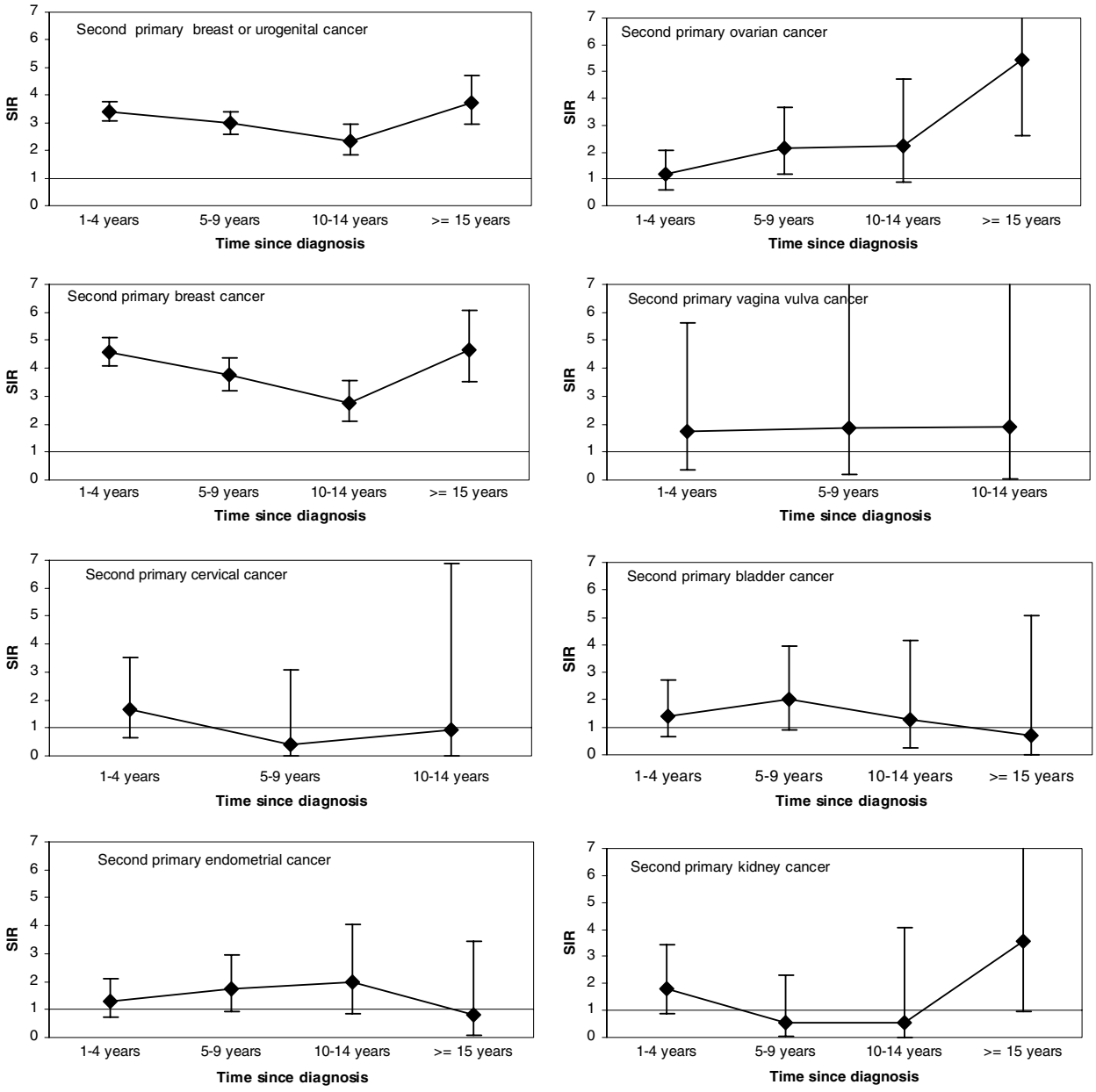

Fig. 1. Standardised incident ratio (SIR) with 95% confidence interval (CI) for second primary breast cancer and urogenital cancer diagnosed in 1972–2001 among breast cancer patients in the south of The Netherlands, diagnosed 1972–2000.

6.1) (Fig. 1). The SIR for ovarian cancer increased after 5–9 years of follow-up (SIR 2.2 95% CI 1.2–3.7) and again after 15 years of follow-up (SIR 5.5 95% CI 2.7–10.4). The SIR for cervical, endometrial, vagina-vulva, kidney and bladder cancer did not vary according to follow-up time. However, after 5 years of observation, the SIR for cervical cancer remained below 1.

4. Discussion

Our results suggest that women diagnosed with a primary breast cancer are at increased risk of developing a second breast and ovarian cancer. This is in line with previous studies [1,4–6,16,17]. Elevated risks were particularly marked among pre-menopausal women. In the south of The Netherlands (area of Eindhoven Cancer Registry), every year 11 of every 1000 breast cancer patients develop a second cancer (I. Soerjomataram, Netherlands Institute of Health Sciences), half of which are second primary breast cancers. Common risk profiles, side-effects of the initial breast cancer treatment and genetic factors have been proposed to cause the elevated risk of second female cancer in breast cancer patients.

Age at first breast cancer diagnosis is an important determinant of the incidence of second breast and

ovarian cancers: the risk for women diagnosed before the age of 50 years was significantly higher than that observed for those diagnosed at older ages, as reported in previous studies [6,18]. This highlights the importance of female hormones in the pathogenesis of second breast and ovarian cancer. Nonetheless, other common risk factors, which initially induced the breast cancer, may also be involved in the aetiology of the second breast cancer, including genetic factors. BRCA1 and BRCA2 mutation would explain 5–10% of breast and ovarian cancer cases [19,20].

Age at breast cancer diagnosis was closely related to the treatment choice. A higher risk of second uterine cancer in post-menopausal breast cancer patients taking on hormonal therapy was found, as has been reported by other authors [11,17]. Tamoxifen, a hormonal therapy, which has been widely used since the late 1980s for post-menopausal women, has been suggested to cause the increase in uterine cancer in breast cancer patients, although controversy exists [4,10]. In our study we found a decreased risk of second endometrial cancer after 15 years of follow-up, which might suggest a latency period of less than 15 years for tamoxifen to induce second endometrial cancer.

However, the risk of second breast cancer among post-menopausal breast cancer patients who received tamoxifen was lower in comparison with that for women who underwent surgical treatment (SIR 1.6 *versus* 2.8). In addition to the side-effects of tamoxifen in inducing cancer of the uterine, some potential beneficial effects in post-menopausal breast cancer patients are now being examined: for example, the anti-oestrogenic role of tamoxifen in mammary cells was found to protect against second breast cancer [9,21].

We found an elevated risk of second breast cancer during the total follow-up period. It has been reported that after radiation there is a latency period of at least 10 years [22]. During the last decades, both radiotherapy and chemotherapy for breast cancer treatment have improved. This includes lower radiation dose, better protection of the normal tissue and more effective polychemotherapy regimens. These changes have diminished some side-effects of radiotherapy in breast cancer patients [22]. Our result supported this fact by showing no difference in second breast cancer risk between women who underwent surgery or radiotherapy.

We observed declining risks of cervical cancer during the follow-up period, which reached 0 in the last follow-up period. This may be related to the human papilloma virus's (HPV) latency period of ±17 years (the time needed from infection to formation of invasive cancer) [23], suggesting sexual behaviour changes among women with breast cancer. Some authors have also noticed the lowered risk of cervical cancer among breast cancer patients [2,5,18,24]. In contrast to cervical cancer, breast cancer is observed more often among women with a higher socio-economic position and among women who had their first child at an older age [25,26]. This may also relate to the lower risk of cervical cancer in breast cancer patients.

During 28 years of follow-up only six patients developed carcinoma of the vagina and vulva. These cancers are rare and represent only 7–8% of gynaecological cancers [25]. Consequently, we could not draw any conclusion about the association between breast cancer and cancer of the vagina and vulva. However, vagina-vulva cancer has been related to HPV infection. The risk of second vagina-vulva cancer became 0 after a follow-up of more than 15 years, as found for second cervical cancer in our study. This suggests a possible inverse relationship between breast cancer and second vagina-vulva cancer. Breast cancer patients may change their lifestyle towards a healthier one that protects against vagina-vulva cancer.

We could not find an excess risk for second primary kidney or bladder cancer after breast cancer. A few studies found a slightly increased risk of second kidney and bladder cancer among breast cancer patients [6,7]. Elevated kidney and bladder cancer risk was found for women receiving high radiation exposure in the pelvic area, such as radiotherapy for cervical cancer [27]. The bladder is one of the organs that receives a considerable amount of scattered radiation during radiotherapy for breast cancer treatment [28]. However, this seems to be insufficient to induce bladder or kidney cancer.

We could not collect information for some of the main risk factors, such as reproductive characteristics or lifestyles of the patients, and did not adjust for potential confounders or effect modifiers. Also, there may be some bias caused by metastases of the primary breast cancer. We expect this bias to be minimal because trained personnel from the cancer registry checked each patient's medical record.

In conclusion, our results show that breast cancer patients are at increased risk of developing second breast and ovarian cancer. Initial breast cancer treatment plays a limited role in causing second breast cancer, suggesting a larger role for common risk factors that induce both primary and second primary breast cancer. This emphasises the importance of behaviour modification among breast cancer patients, as well as the use of monitoring in order to prevent increased morbidity and mortality caused by second breast cancer. As for second ovarian cancer, women diagnosed with breast cancer before menopause may benefit from a longer follow-up directed to the early detection of second ovarian cancer. As our understanding of the relationship between risk factors and the occurrence of a second cancer develops, more questions will arise. Thus, extensive studies on multiple cancers will continue to play an important role in the medical sciences. Such studies may serve as a foundation for understanding the environmental and genetic determinants of cancer.

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