THERAPEUTIC ADVANCES in
Medical Oncology

Review

Risk of second primary cancer in young breast cancer survivors: an important yet overlooked issue

Xinyi Liang, Yiwei Qin, Pengwei Li, You Mo* and Dawei Chen*

Ther Adv Med Oncol

2025, Vol. 17: 1–15

DOI: 10.1177/17588359251321904

***Abstract*:** Currently, female breast cancer (BC) represents the highest incidence of cancer globally. This trend has raised significant attention regarding breast cancer young women (BCYW). With advancements in treatment technology, BCYW survivors are living longer; however, the risk of developing or succumbing to a second primary cancer (SPC) has greatly increased. In addition, several factors, including age, menstrual cycle, hormonal changes, obesity, pregnancy, and breastfeeding, interact to influence the development of SPC in BCYW and make its treatment more difficult. This study investigates the relationship between BCYW and SPC, focusing on morbidity trends, pathological genomics, recurrence rates, survival times, treatment modalities, and physiological fertility. Most BCYW involve BRCA pathogenic variants or fall under triple-negative and human epidermal growth factor receptor 2-overexpressing subtypes, increasing the risk of SPC. While there are regional variations in survival time following the diagnosis of an SPC, the long-term survival outcomes remain unfavorable. In addition, the choice of treatment for BCYW survivors has a prolonged cumulative toxic effect. The combination of endocrine therapy and chemotherapy is effective in treating BC, but it simultaneously increases the risk of developing an SPC, specifically endometrial cancer. Furthermore, radiotherapy is associated with a heightened risk of contralateral BC and lung cancer. We aim to address existing gaps in the literature and to enhance awareness of the risks associated with SPC in BCYW, thereby offering valuable insights for clinical diagnosis and treatment.

Keywords: breast cancer, incidence, second primary cancer, survival, therapy, young women

Received: 26 November 2024; revised manuscript accepted: 4 February 2025.

Correspondence to:

You Mo
Department of Cardiovascular Medicine, The First Affiliated Hospital of Shantou University Medical College, Shantou University, No.57, Changping Road, Shantou, Guangdong 515000, People's Republic of China
moyou.moyou@163.com

Dawei Chen
Department of Shandong Provincial Key Laboratory of Precision Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Huaiyin District, Jinan, Shandong 250000, People's Republic of China
dave0505@yeah.net

Xinyi Liang
School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, People's Republic of China

Department of Shandong Provincial Key Laboratory of Precision Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, People's Republic of China

Yiwei Qin
Department of Shandong Provincial Key Laboratory of Precision Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, People's Republic of China

Department of Radiation Oncology, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, People's Republic of China

Introduction

Breast cancer (BC) has surpassed lung cancer to become the most common cancer worldwide and the fourth leading cause of cancer death.[1] Surprisingly, the rise in BC incidence is mostly observed in younger women. Studies show that BC rates in women <40 years old are steadily increasing,[2,3] with nearly a 2% annual rise among those aged 20–29, and a 0.2% increase per year for women in their 30 years old. Fortunately, with the diversification of treatments and the maturity of imaging equipment, the proportion of BC survivors has increased.[4,5] Nevertheless, it is important to recognize that while breast cancer survivors live longer, they face a significantly higher risk of developing or dying from a second cancer.[4,6] In addition, the long-term nature of treatment and complications in younger patients significantly increase the risk of an SPC compared to older women with BC.[7,8]

Based on epidemiological data, approximately 12.30% of breast cancer in young women (BCYW) develop second primary cancer (SPC).[9] Among these, second primary breast cancer (SPBC) accounts for nearly one-third of all SPC, second only to the initial primary breast cancer (PBC).[10] Notably, contralateral breast cancer (CBC) is particularly common.[11] However, women with BC in Europe[12] and the United

Pengwei Li
Department of Shandong Provincial Key Laboratory of Precision Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, People's Republic of China

*These authors have contributed equally to this work.

States[13] face a 20%–30% higher risk of developing a second non-breast primary cancer. Regarding the location of SPC, research from the Surveillance, Epidemiology, and End Results (SEER) database in the United States in 2019 indicates that the most common site for an SPC in female BC patients is the contralateral breast,[14] followed by uterine cancer,[15] ovarian cancer,[16] lung cancer,[17] stomach cancer, colorectal cancer,[18] thyroid cancer,[15,19] and acute myeloid leukemia.[20] It is evident that with the long-term effects of BC treatment, the risk of developing SPC increases,[21] with contralateral second primary breast cancer being more common.

The rate of young-onset BC has been rising each year, along with the risk of SPC. Studies suggest this is linked to tumor size, germline pathogenic variants (PVs),[22] and family history.[23] Despite these risk factors, there is no systematic study describing the biological behavior and treatment-related risks of BCYW and SPC. This paper aims to comprehensively elaborate the incidence, pathological molecular subtypes, survival, susceptibility genes, treatment, and reproductive outcomes in BCYW with SPC, addressing gaps in current research. It highlights the importance of focusing on SPC in BCYW to provide valuable guidance for clinical diagnosis and treatment.

Increasing incidence trends of BCYW and SPC

Globally, the incidence of BCYW is on the rise,[24] with approximately 25% of cases occurring in women under the age of 50.[25] Experts generally agree that BCYW should be defined as occurring in women under 40 based on clinical and biological characteristics.[26] A U.S. study of 134,518 women under 40 with BC across 42 states found the highest average annual percentage change (AAPC = 1.00%) in Asian Pacific American women, followed by non-Hispanic white women (AAPC = 0.50%) and non-Hispanic black women (AAPC = 0.30%; Table 1).[27] In a 20-year retrospective study of BCYW in China, the age-standardized percentage (ASP) of cases under 35 rose from 4% in 2000 to 5.9% in 2017, with incidence increasing by about 2% annually.[28] In France, the highest increase in incidence was seen in younger BC patients, with an AAPC of 2.10%.[29] In Iran, the rise in BC incidence primarily stems from the younger age group. The AAPC in the 20–29 age group (AAPC = 10.0) is twice as high as that in the 30–39 age group (AAPC = 5.10).[30,31] In a study on young BC in West Africa (Gambia), the AAPC for women aged 50 and older was 1.30%, while the AAPC for women under 50 reached 7.6%. It is clear that the annual growth rate of BC incidence is higher in women aged 50 and under compared to those over 50.[32] Overall, the average annual increase in BCYW incidence is at least 2% (Figure 1), with the highest incidence observed in the 30–35 age group. Young BC is the primary concern for women under 40, and the issues of recurrence and the risk of SPC also pose urgent challenges.

According to research, women younger than 40 years of age have a higher risk of local recurrence and distant metastasis than older women.[46] In a review of recurrence risk in BCYW, the median cumulative recurrence rate (MCRR) over 5–10 years of ipsilateral BC was 3.10%, and the 10-year MCRR was 7.90%.[33] Obviously, young BC has a higher risk of recurrence within 10 years; however, the occurrence of an SPC is often overlooked. In the United States, the 5-year cumulative incidence (CI) of an SPC in BC is 0.89% (Table 2).[47] Another study of BC patients found racial and ethnic differences in the risk of developing an SPC. Asian American, Native Hawaiian, or other Pacific Islander (standardized incidence ratio, SIR = 1.49), Black (SIR = 1.41), and Latino women (SIR = 1.45) had a 40%–49% higher risk of developing a second cancer, while white women had a lower but still 9% higher risk compared to the general population (SIR = 1.09).[48] SIR is a relative index obtained by comparing the actual incidence rate of a specific population with the expected incidence rate. The expected incidence rate is calculated based on the incidence rate of a standard population. The SIR can help assess whether the incidence of a specific population is higher or lower than that of the standard population.[48,49] In a study of 53,783 female BC patients in Taiwan, the overall 5-year SIR of second primary non-breast cancer (SPNBC) was 1.09, with no increase in patients over 50 but a significant rise in those under 50 (SIR = 1.43).[50] Studies in northern Portugal found that patients with a first PBC had an SIR of 1.36 for all types of SPC and an SIR of 9.72 for SPC that occurred simultaneously, meaning those diagnosed within a short period (usually within 2 months) after the first PBC diagnosis.[51] The SIR of SNBC within 10 years in Korean breast cancer patients was 5.78.[52] Studies from the four regions mentioned above revealed that the 5-year SIR of SPC in BCYW ranged from 1.36 to 1.50 (Figure 2). The occurrence of SPC in BCYW was more

Table 1. Summary of partial characteristics of breast cancer in young women.

Variables	Origin of cancer registry	Status and characteristics in BCYW	Date	Number of patients	References
Incidence	USA	AAPC = 1.0% (APA women), AAPC = 0.5% (NHW women), AAPC = 0.3% (NHB women)	2001–2015	134,518	27
	China	ASP increased from 4.0% to 5.9% from 2000 to 2017, with an annual increase of 2.0%	2000–2017	1,308	28
	France	AAPC = 2.1%	1999–2018	N/A	29
	Iran	AAPC = 10.0% (20–29 age group), AAPC = 5.1% (30–39 age group)	2004–2013	2,106	30
	Africa	AAPC = 7.6% (in BCYW), AAPC = 1.3% (in older women)	1990–2014	N/A	32
Recurrence or metastasis	Multiple Countries	MCRR = 3.1% (in 5–10 years), MCRR = 7.9% (in 10 years)	1980–2009	N/A	33
Molecular subtype	China	TNBC = 18.1%, HER2/neu overexpression = 8.0%	2004–2014	24,474	34
	Mexico	TNBC = 37.1%, Luminal A = 37.1%, HER2 = 13.5%, Luminal B = 12.2%	2012–2017	282	35
	Switzerland	TNBC = 10.4%, Luminal A = 32.8%, Luminal B = 37.5%	1970–2012	1,586	36
Survival time	USA	5-year OS = 90.0%, BCSS = 91.2%, HR+ HER2– BCSS = 92.9%, TNBC BCSS = 81.7%	2010–2018	18,400	37
	China	5-year OS = 93.9%, BCSS = 94.2%, HR+ HER2– BCSS = 96.3%, TNBC BCSS = 88.0%	2008–2019	2,459	37
	Switzerland	10-year OS = 68.0%, 10-year DFS = 68.0%, 20-year DFS = 60.0%	1970–2012	1,586	36
	USA	10-year OS = 73.0%, 10-year DFS = 48.0%	1990–2010	529	38
	Multiple Countries	8-year DFS (HER2–) Luminal B = 69.0%, Luminal A = 62.0%, TNBC = 63.0%	2000–2020	3,547	39
	Multiple Countries	8-year DFS HR+ = 65.8%, HR– = 63.4% 8-year OS HR+ = 88.1%, HR– = 87.1%	2000–2020	4,718	40
		8-year DSF Luminal B = 69.7%, Luminal A = 60.8%, TNBC = 63.5%, HER2+ = 65.5%			
		8-year OS Luminal B = 90.1%, Luminal A = 87.8%, TNBC = 87.0%, HER2+ = 87.2%			
Susceptibility gene	UK	BRCA 12.0% BCYW (<40 years)	N/A	2,733	41
	USA	BRCA 9.4% BCYW (⩽35 years)	1990–1992	203	42
	SOFT Clinical Trial	Higher GATA3 PVs 19.0% and copy number 47.0%, lower PIK3CA PVs 32.0%, CDH1 PVs 3.0%, MAP3K1 PVs 7.0%	N/A	1,276	43
Therapy	USA	CRRS increased from 10.0% in 2004 to 33.0% in 2012	2004–2012	1,224,947	44
	Multiple Countries	OFS or ovarian elimination reduces 15-year recurrence risk, BCSS, and OS	1995–2000	N/A	45

AAPC, average annual percentage change; APA women, Asian Pacific American women; ASP, annual standard percentage; BCSS, breast cancer-specific survival; BCYW, breast cancer in young women; CRR, cumulative relapse rate; CRRS, contralateral risk reduction surgery; DFS, disease-free survival; HER2–, human epidermal growth factor receptor 2 negative; HER2+, human epidermal growth factor receptor 2 positive; HR, hazard ratio; HR+, hormone receptor-positive; HR–, hormone receptor-negative; HR+ HER2–, hormone receptor-positive and human epidermal growth factor receptor 2 negative; MCRR, median cumulative recurrence rate; NHB women, non-Hispanic Blacks women; NHW women, non-Hispanic White women; OFS, ovarian function suppression; OS, overall survival; PVs, pathogenic variants; TNBC, triple-negative breast cancer.

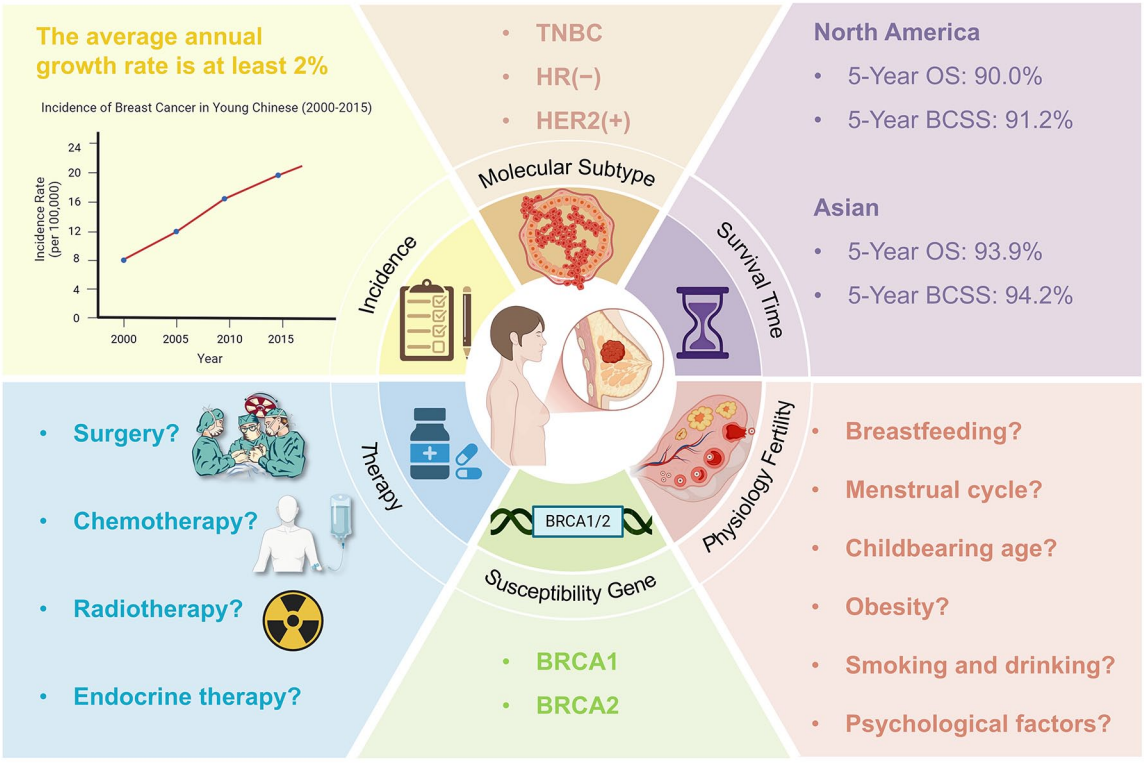

Figure 1. High-risk factors for breast cancer in young women. Analysis and summary of high-risk factors in the incidence, molecular subtype, survival time, therapy, susceptibility genes, and physiological fertility in young breast cancer patients.
Source: Some elements in the figure (such as characters and icons) were created using BioRender.
BCSS, breast cancer-specific survival; HER2+, human epidermal growth factor receptor 2; HR–, hormone receptor-negative; OS, overall survival; TNBC, triple-negative breast cancer.

prominent in the United States and South Korea. Several studies analyzed the interval times between the first BC and SPC; a Canadian study (2006–2016) found a median interval of 7.3 years.[53] Similar findings were observed in the Korean study, young BC patients developed a SPC within 7.61 years of their primary BC diagnosis.[52] In a U.S. cohort of 3223 women with BC, 719 SPC cases were detected over an average follow-up of 11.2 years. This indicates that most SPCs were diagnosed within 10 years.

In summary, the incidence of young BC is high, and the risk of recurrence within 10 years is also elevated. While there is no significant variation in the 5-year SIR of SPC among BCYW across different countries, all rates are increasing. Most SPCs occur within 10 years after the first diagnosis.

Molecular subtypes impact BCYW and SPC

Across various studies, 34%–54% of women diagnosed with BCYW have been found to have TNBC.[40] In a study, very young BC patients exhibited a higher incidence of TNBC subtypes (18.10% vs a mean of 8.60%), and an increased rate of HER2 overexpression (8.00% vs a mean of 6.40%).[34] Furthermore, a study on molecular subtyping of BCYW in Mexico found that the incidence of TNBC and Luminal A was the highest, both at 37.14%. By contrast, the incidence of the HER2 subtype was lower at 13.47%, and Luminal B occurred at a rate of 12.24%.[35] Nonetheless, a study in Switzerland found that most patients were diagnosed with the molecular subtypes Luminal A and Luminal B, at 32.8% and 37.5% respectively. By contrast, TNBC comprised only 10.40% of tumors, making it the least prevalent subtype.[36] The above studies fully confirmed that the molecular subtypes of BCYW are mostly TNBC or HER2 overexpression types, and the other types also exist but account for a relatively small and uncommon proportion.

BCYW are more likely to develop SPC because their molecular subtypes are often TNBC, HER2

Table 2. Summary of partial characteristics of breast cancer in second primary cancer.

Variables	Origin of cancer registry	Status and characteristics in SPC	Date	Number of patients	References
Incidence	USA	CIR = 0.89% (within 5 years)	1990–2019	416,566	47
	USA	SIR = 1.49 (AANHPI women), SIR = 1.41 (Black women), SIR = 1.45 (Latina women), SIR = 1.09 (White women)	2000–2017	717,335	48
	China	SPNBC SIR = 1.09 (within 5 years)	1979–2003	53,783	50
	Portugal	SIR = 1.36	2000–2010	15,981	51
	Korea	SPNBC SIR = 5.78 (within 10 years)	2003–2008	52,506	52
Molecular subtype	Korea	TNBC 10-year CI = 12.4%, HER2/neu overexpression 10-year CI = 6.1%, HR+ 10-year CI = 4.8%	1999–2013	16,251	54
	USA	TNBC with SPC (HR = 1.77, 95% CI, 1.46–2.15), HER2/neu overexpression with SPC (HR = 1.37, 95% CI, 0.99–1.89)	1990–2010	250,764	55
	UK	HER2+ with SPC (HR = 0.93, 95% CI, 0.89–0.97)	1995–2019	281,403	56
Survival time	USA	20-year OS = 49.21%, 15-year OS = 66.16%, 10-year OS = 85.77%	1990–2010	250,764	55
	China (Shanghai)	15-year OS = 56.44%, 10-year OS = 64.42%, 5-year OS = 88.34%	2002–2015	163	57
	China (Taiwan)	15-year OS = 23.00%, 10-year OS = 30.00%, 5-year OS = 40.00%, 1-year OS = 71.00%	1979–2003	53,783	50
	Korea	5-year OS = 62.28%	2003–2008	52,506	52
Susceptibility gene	Multiple countries	5-year CR BRCA 1 = 15.00%, BRCA2 = 9.00%, 10-year CR BRCA1 = 27.00%, BRCA2 = 19.00%	1975–2011	4,693	58
	China	10-year CR BRCA1 = 15.50%, BRCA2 = 17.50%, 10-year CR BRCA1 = 21.50% (≤ 40 years)	2003–2015	9,401	59
	USA	Germ line PVs carrier 5-year CR = 5.50%, 10-year CR = 8.90%	2006–2015	1,279	60
Therapy	USA	10-year CRRS with SPC = 0.93%, UM with SPC = 4.44% 15-year CRRS with SPC = 1.15%, UM with SPC = 7.77%	1998–2013	180,068	61
	UK	Hormonotherapy SIR = 2.30, without Hormonotherapy SIR = 1.95	1995–2019	281,403	56
	USA	Radiotherapy with higher SPC (SHR = 1.16), chemotherapy with lower SPC (SHR = 0.88)	2000–2015	9,247	62
	Multiple countries	Radiotherapy with lung cancer (SHR = 1.11), with breast cancer (SHR = 1.39), with AML (SHR = 1.30)	N/A	N/A	63–66
	Multiple countries	Radiotherapy ATM with rare missense variant = 16.00% (10-year CR)	1985–2000	2,107	67
	USA	Chemotherapy with lung cancer (SHR = 0.90), with breast cancer (SHR = 0.89)	2001–2014	442,234	68

CIR, cumulative incidence rate; CR, cumulative risk; CRRS, contralateral risk reduction surgery; HR, hazard ratio; OS, overall survival; PVs, pathogenic variants; SHR, sub-hazard ratio; SIR, standardized incidence rate; SPC, second primary cancer; SPNBC, second primary non-breast cancer; TNBC, triple-negative breast cancer; UM, unilateral mastectomy.

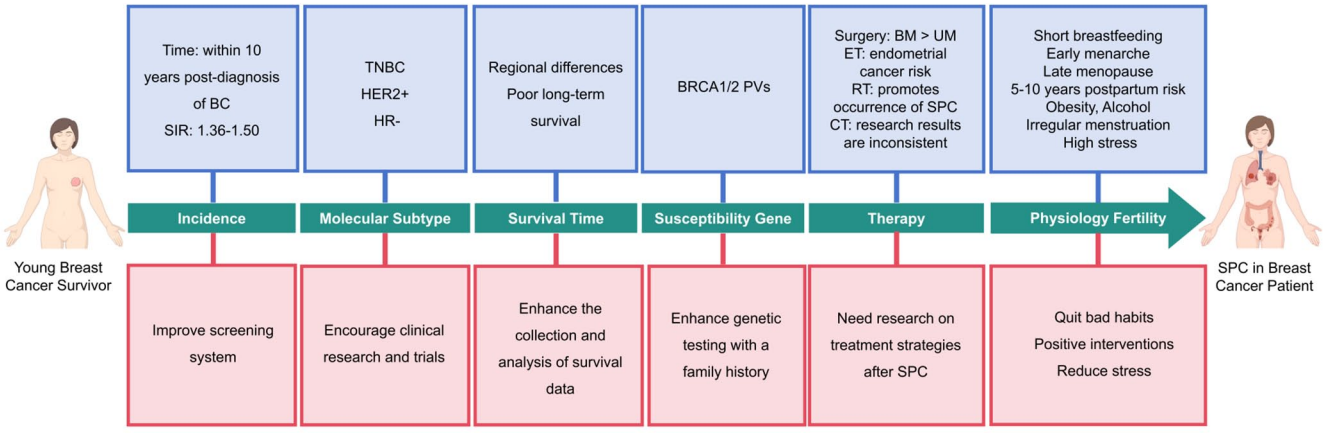

Figure 2. Risk factors and solutions for the development of a second primary cancer. Summary of the highest risk factors of young breast cancer survivors and preventive measures, based on six areas, incidence, molecular subtype, survival time, therapy, susceptibility gene, and physiological fertility.
Source: Some elements in the figure (such as characters) were created using BioRender.
BC, breast cancer; BM, bilateral mastectomy; CT, chemotherapy; ET, endocrine therapy; HER2+, human epidermal growth factor receptor 2; HR–, hormone receptor-negative; PVs, pathogenic variants; RT, radiotherapy; SIR, standardized incidence ratio; SPC, second primary cancer; TNBC, triple-negative breast cancer; UM, unilateral mastectomy.

overexpression, or HR–. For young patients with TNBC, a study conducted in Korea revealed that this subtype was linked to the highest incidence of CBC. Specifically, the 10-year CI of CBC was 12.40% in the TNBC group and the 10-year CI of CBC associated with HER2 overexpression was 6.10%. The incidence of HR+ BC was notably lower than that of the first two molecular subtypes, with rates of 4.80% and 2.70%, respectively ($p = 0.002$).[54] Similarly, multiple studies in the United States have found that TNBC significantly increased the risk of CBC (HR = 1.77, 95% CI = 1.46–2.15).[55,69] HER2 overexpression in the first BC was strongly associated with an increased risk of CBC (HR = 1.37, 95% CI = 0.99–1.89). This finding suggests that HER2 overexpression and TNBC in young women in the United States carry a high risk of developing an SPBC.[55] In the British HER2-positive study, the results were inconsistent. Young patients with HER2+ BC exhibited a 7% lower risk of developing an SPNBC (HR = 0.93, 95% CI = 0.89–0.97).[56] In summary, the molecular subtypes TNBC, HER2 overexpression, and HR-negative are closely associated with the occurrence of SPC.

Poor survival of SPCs in long-term survivors of BCYW

Survival time of BCYW

The survival time of BCYW and the prognosis of the SPC have become the focus of attention. The high tumor burden, advanced stage, and greater aggressiveness in BCYW increase the risk of SPC and impact patient survival.[38] Two studies compared survival outcomes between young Chinese women and white American women with BC (Figure 1). The results showed that the white American women had lower 5-year overall survival (OS; 90.00% vs 93.90%, $p < 0.001$) and breast cancer-specific survival (BCSS; 91.20% vs 94.20%, $p < 0.001$).[37] Similarly, it was observed that the 5-year BCSS in young Chinese women was significantly higher than in young white women for both HR+/HER2-and TNBC (96.30% vs 92.90%, $p < 0.001$; 88.00% vs 81.70%, $p = 0.006$).[37] However, a study conducted in Switzerland reported longer survival times. The 10-year OS for young BC patients was approximately 68%, with a 10-year disease-free survival (DFS) rate of 68% (95% CI = 0.66–0.71). After 20 years, the DFS rate dropped to 60% (95% CI = 0.57–0.63).[36] In a similar study, it was found that the 10-year OS rate for BC patients aged 35 and younger was 73%, while the 10-year DFS rate for this age group was 48%.[38] For BCYW, the 10-year OS is about 70%, and young Chinese women have better survival benefits than American women in both OS and BCSS.

Further molecular subtype studies have found that Luminal B and HR+ subtypes offer better survival benefits. In the HER2-negative group, Luminal B demonstrated the most favorable prognosis, with an 8-year DFS of 69% (95%

CI = 64%–73%), compared to 62% (95% CI = 54%–69%) for Luminal A and 63% (95% CI = 60%–66%) for TNBC, respectively.[23] Another study showed that HR+ patients have a better prognosis than HR–, in terms of OS, recurrence, or progression time. HR+ patients 8-year DFS rate was 65.80% (95% CI = 63.40%–68.20%), compared to 63.40% (95% CI = 61.20%–65.60%) for HR– patients. The 8-year OS rate was 88.10% (95% CI = 86.30%–89.70%) for HR+ patients, while for HR– patients, it was 87.10% (95% CI = 85.50%–88.50%).[40] In a global multicenter retrospective study that evaluated the 8-year OS, BCSS, and PFS across different molecular subtypes, the 8-year DFS rates were as follows: Luminal A: 60.80% (95% CI = 55.70%–65.40%), Luminal B: 69.7% (95% CI = 66.20%–72.80%), TNBC: 63.5% (95% CI = 61.10%–65.70%), and HER2+: 65.50% (95% CI = 59.10%–71.10%). In addition, the 8-year OS rates were as follows: Luminal A at 87.80% (95% CI = 83.90%–90.80%), Luminal B at 90.10% (95% CI = 87.70%–92.00%), TNBC at 87% (95% CI = 85.40%–88.50%), and HER2+ at 87.20% (95% CI = 82.10%–90.90%). These findings suggest that BCYW with the Luminal B subtype tend to have better prognoses, with similar outcomes observed among BRCA mutation carriers.[40] The study indicated that shorter survival times in BCYW were linked to a higher risk of recurrence or progression. Among these patients, those with Luminal B or HR+ subtypes had better OS, PFS, and BCSS. In the long-term treatment of BCYW, it is crucial not only to actively manage the primary tumor but also to remain vigilant about the impact of SPC on subsequent survival.

Survival time of SPC

Chinese research data show that the incidence of SPC in BCYW is 2.20% at 5 years and 4.40% at 10 years.[38] There was a notable difference in OS between patients with and without SPC (10 years: 85.77% with SPC vs 86.37% without; 15 years: 66.16% vs 74.39%; 20 years: 49.21% vs 74.39%). Patients with a SPC had much worse long-term survival compared to those without.[55] In addition, the survival time of patients with a SPC varies in different regions. In a small sample study of 163 cases in Shanghai, China, it was found that the 5-year, 10-year, and 15-year OS rates of BCYW with an SPC were 88.34%, 64.42%, and 56.44%, respectively.[52] Similarly, in a study of 53,783 BCYW in Taiwan, 1-year, 5-year, 10-year, and 15-year survival rates for patients with a SPC were 71%, 40%, 30%, and 23%, respectively.[50] By contrast, in a Korean study of 52,506 women with BC, the 5-year OS rate for BCYW with an SPC was significantly higher than in Taiwan, China, at 62.28% (95% CI = 65.53–69.02).[52] In patients with SPC, the 5-year OS is highest for thyroid cancer (5-year OS = 89.6%), followed by cervical cancer (5-year OS = 75.3%) and colorectal cancer (5-year OS = 73.9%). However, the lowest 5-year OS among second primary cancers is observed in lung cancer (5-year OS = 21.5%).[70] Although survival time after developing an SPC in BCYW varies by region, long-term survival outcomes are generally poor. This makes SPC the second leading cause of death for BCYW, after the primary cancer itself.

Genetic susceptibility implies the risk of BCYW and SPC

BRCA1/2 PVs are the most common individual mutations in familial breast cancer, increasing the risk of developing BC by 3–5 times.[71] BCYW <50 years tend to be more aggressive and advanced, often linked to inherited PVs, such as those in the BRCA gene.[59,69] One study found that approximately 12% of BCYW < 40 years of age are associated with germline PVs in the BC susceptibility genes BRCA1/2.[41,72] Even in another study, very young BC (age ⩽ 35) were found to have a 9.4% chance of having a detectable BRCA1/2 PVs.[42,73] Compared to older women (⩾ 40 years), HR+ HER2− early BC in younger women shows distinct genomic characteristics. These include a higher frequency of GATA3 PVs (19% vs 16%) and copy number amplifications (47% vs 26%), but a lower frequency of PIK3CA (32% vs 47%), CDH1 (3% vs 9%), and MAP3K1 (7% vs 12%) PVs. However, most BC carry pathogenic mutations in only one gene, and the co-occurrence of germline PVs in both BRCA1 and BRCA2 is rare.[39]

Similarly, studies on SPBC are more common in carriers of BRCA1 or BRCA2 PVs.[41] Several studies have shown that BRCA1 PV carriers have a cumulative risk of CBC of 15% at 5 years, rising to 27% at 10 years. In BRCA2 PV carriers, the cumulative risk of CBC is 9% at 5 years, increasing to 19% at 10 years. The 5-year cumulative risk of developing an SPC is approximately five times higher in women with BRCA1 mutations and three times higher in those with BRCA2 PVs compared to non-carriers. Moreover, Peking

University Cancer Hospital conducted a study on the 10-year cumulative risk of CBC in BC patients with BRCA PVs. The 10-year cumulative CBC risk was 15.5% (95% CI = 9.99–24.20) for BRCA1 PVs carriers, 17.5% (95% CI = 10.90–28.00) for BRCA2 carriers, and 3.20% (95% CI = 2.50–4.10) for non-carriers. In addition, BRCA1 PV carriers first diagnosed with BC at or before age 40 had a significantly higher 10-year cumulative risk of CBC (21.50% vs 11.90%; $p = 0.044$).[59] Similarly, a recent 10-year study in the United States found that the 5-year risk of SPBC in germline PV carriers was 5.50% (95% CI 1.60%–19.60%), and the 10-year risk was 8.90% (95% CI = 2.60%–30.30%). These rates were significantly higher compared to non-carriers, whose 5-year risk was 1.30% (95% CI = 0.70%–2.60%) and 10-year risk was 2.20% (95% CI = 1.20%–4.00%).[61] Thus, approximately 12% of BCYW cases are linked to germline PVs in BRCA1 or BRCA2. Moreover, the cumulative risk of developing a SPC increases almost exponentially every 5 years.

Therapy associated with BCYW and SPC

Surgery and SPC risk

BC treatment options include surgery, radiotherapy (RT), chemotherapy (CT), endocrine therapy (ET), and targeted therapy. Younger patients or those with large, aggressive tumors are more likely to undergo mastectomy and contralateral risk reduction surgery (CRRS).[74,75] A U.S. study found a rapid increase in the rate of CRRS, rising from 10% in 2004 to 33% in 2012 among women aged 20–44, and from 4% to 10% in women aged 45 and older during the same period. This indicates that younger women with BC are increasingly opting for mastectomy combined with CRRS to reduce the risk of future recurrence.[44] A Korean study found that surgery for PBC at age ⩽ 35 (hazard ratios, HR = 2.49) doubled the risk of developing CBC.[54] Ten years after BC surgery, the incidence of an SPC was 0.93% in the CRRS group, compared to 4.44% in the unilateral mastectomy (UM) group, with bilateral Mastectomy (BM) reducing the risk by approximately 78.50%. After 15 years, the incidence increased to 1.15% in CRRS patients and 7.77% in UM patients.[61] While BM reduces the risk of recurrence and SPC, patients still face a certain level of risk. Within the first 10 years, this approach provides better outcomes compared to UM, benefiting both the primary cancer and SPC. However, after 15 years, the risk of developing a SPC following BM becomes more pronounced.

Endocrine therapy and SPC risk

Furthermore, elevated estrogen levels in women can also result in the abnormal proliferation of breast ducts, which may ultimately lead to BC.[76] Therefore, approximately 70% of patients with HR+ BC can achieve antitumor effects by reducing estrogen levels through ET.[77,78] Similarly, a 2023 EBCTCG meta-analysis further confirmed that OFS or ovarian ablation significantly reduced the 15-year recurrence risk, breast cancer-specific mortality, and overall mortality.[45] In patients aged ⩽ 35 years, the combination of aromatase inhibitors and OFS resulted in better 12-year DFS and it may also provide an OS benefit.[79] However, multiple studies have indicated that the use of AIs in postmenopausal BC patients may not sufficiently suppress estradiol and estrone levels.[80,81] Consequently, this inadequacy can lead to an increased risk of SPBC events, particularly among tamoxifen-treated patients with a history of uterine cancer.[82] A study in the UK showed that women with BC with HT (SIR = 2.30, 95% CI = 2.21–2.40) had a higher SIR than those without HT (SIR = 1.95, 95% CI = 1.86–2.04). In the era of widespread use of ET, the incidence of second primary endometrial cancer in BC patients receiving HT has significantly increased.[56] ET has varying effects depending on the site of action. Studies have demonstrated that the incidence of CBC in patients treated with tamoxifen for 5 years progressively decreases over a 30-year follow-up period. Patients who received tamoxifen for 5 years experienced an increased incidence of endometrial cancer. Conversely, the incidence of lung cancer, especially small-cell and squamous-cell lung cancers, was reduced in this treatment group.[83] Indeed, ET has a dual effect on patients with early-stage BC. On one hand, it can inhibit estrogen resistance in PBC, and on the other hand, it helps reduce the risk of an SPBC, providing a protective role against secondary tumors.[84]

Radiotherapy and SPC risk

RT has the potential to lead to the development of SPC through ionizing radiation. Therefore, it is considered a risk factor for tumor occurrence and progression. Survivors with RT have a higher risk of developing SPC (SHR = 1.161, 95%

CI = 1.109–1.217, $p < 0.001$). By contrast, patients only with CT have a slightly reduced risk of developing SPC (SHR = 0.880, 95% CI = 0.832–0.931, $p < 0.001$).[62] However, when chest RT is added to CT, the adverse effects of radiation gradually appear. In addition to the risk of leukemia and myelodysplastic syndromes,[85,86] the risk of developing SPC in irradiated areas is significantly increased.[52,87] Studies show that RT patients have an elevated risk of any SPC, with specific risks for LC (SHR = 1.109; 95% CI = 1.033–1.192; $p = 0.045$), BC (SHR = 1.389; 95% CI = 1.34–1.44; $p < 0.001$), and acute myeloid leukemia (SHR = 1.298; 95% CI = 1.01–1.67; $p = 0.045$), particularly for LC, esophageal cancer, and CBC.[63–65] According to a study conducted in the United States, the CI of NBC SPC >25 years is higher in the RT group compared to the non-RT group for patients of all ages.[88] Patients with rare missense mutations in the ATM gene receive RT and have a higher risk of CBC. Specifically, the 10-year cumulative risk of CBC in these patients is 16% (95% CI = 7.00%–36.50%). By contrast, similar patients not receiving RT have a 10-year cumulative risk of only 2.20% (95% CI = 0.50%–9.00%). This indicates that the risk of CBC increases by approximately seven times for patients carrying rare missense mutations in ATM after receiving RT.[67] The use of RT can indeed lead to the development of SPC. RT kills tumor cells by inducing DNA damage. However, it also harms normal tissues and leads to the development of SPC.

Chemotherapy and SPC risk

In studies related to CT for BC, the results are inconsistent, and there is currently no definitive conclusion. Research indicates that patients undergoing CT experience a diminished likelihood of developing SPC. Specifically, the risk of LC is reduced (SHR = 0.895; 95% CI = 0.818–0.979; $p = 0.015$), and the risk of BC is also lowered (SHR = 0.891; 95% CI = 0.854–0.930; $p < 0.001$). Nonetheless, some studies have reported that the use of CT drugs can damage DNA, leading to an increased incidence of SPC.[68] A study on young women with BC in the UK found differences in the (SIRs for myeloid leukemia related to CT: for those who received CT, the SIR = 2.71 (95% CI = 2.36–3.08), while for those who did not receive CT, the SIR = 1.32 (95% CI = 1.20–1.44).[56] Surprisingly, two other studies showed different results. CT was significantly associated with a reduced BCSS in patients with ER deficiency (HR = 0.51, 95% CI = 0.29–0.90, $p = 0.020$) or PR deficiency (HR = 0.47, 95% CI = 0.28–0.79, $p = 0.004$).[89] In addition, the use of adjuvant CT and ET was associated with a lower risk of CBC.[90]

In summary, questions remain regarding the therapy increase the risk of SPC. BC patients developing SPC after treatment may have a poorer prognosis than those with only BC. As a result, these patients may be unable to tolerate treatment for secondary tumors, and their options for medication are very limited, significantly reducing the effectiveness of treatment for SPC. Future studies in this area need to be strengthened to explore potential risk factors and effective treatment strategies in depth.[70] Based on the above research findings, clinical physicians should take a comprehensive approach when making treatment decisions.

Physiological and reproductive risk factors

The diagnosis of BCYW can be comprehensively analyzed and considered from physiological, reproductive, and psychosocial perspectives. Recent studies indicate that a short duration or lack of breastfeeding (BF), as well as abruptly stopping BF, can increase the risk of BC in young women.[91] The occurrence of BC is closely related to advanced maternal age at first childbirth. Multiple studies have shown that having a first pregnancy at age 35 or older increases the risk of BC.[92,93] Similarly, the postpartum period is a high-risk window with an increased likelihood of developing new cancers and rapidly progressing subclinical metastatic phenotypes.[94] Postpartum breast cancer (PPBC) patients often have a poorer survival prognosis. In a study, the overall mortality risk increased by 1.7 times in the PPBC group with a duration of 5 to less than 10 years (HR = 1.72, 95% CI = 1.17–2.52, $p = 0.006$).[95] In summary, giving birth for the first time after the age of 35, having interrupted or short BF, and being within 10 years postpartum are all associated with the risk of developing a SPC.

In addition, the occurrence of BC is influenced by various factors, including its physiological structure, hormonal changes, unhealthy lifestyle habits, and social psychological stress. The earlier the onset of menstruation, the higher the lifetime risk of BC, increasing by 5% for each year earlier. Similarly, each year, the menopause is delayed, the risk of BC rises by 2.8%–3.5%.[96]

Being overweight or obese, consuming alcohol, having lower fertility rates, experiencing irregular menstruation, and having high social-psychological stress can also contribute to the occurrence and development of BC.[97,98] A study on menstrual cycle irregularity found that women aged 29–46 with irregular menstruation have an 11% higher overall cancer risk than those with regular cycles.[99] As mentioned above, factors such as late age at first pregnancy, short or sudden interruption of BF, early age at menarche, late menopause, a high-risk period postpartum (5–10 years), obesity, alcohol consumption, lower fertility rates, irregular menstruation, and increased social psychological stress contribute to a higher incidence of BCYW. Through the research outlined above, young women can implement control measures or interventions to reduce the risk of developing BC.

Summary and outlook

It is becoming increasingly clear that there is a complex relationship between BCYW and SPC. This study provides a comprehensive analysis of the epidemiology, molecular subtypes, genetic mutations, survival times, treatment methods, and reproductive factors related to both conditions. This article provides the relationship between BCYW and SPC, offering valuable insights for personalized treatment plans, risk assessment, and long-term follow-up in clinical practice.

The occurrence of SPC in BCYW remains a significant global health challenge for women. Despite advances in medical technology, the trend of increasing incidence of BC in younger populations continues to elevate the risk of developing SPC. There are still many gaps in research regarding this issue. To better identify BCYW and avoid late-stage diagnoses due to delayed detection, women $<$40 years should be included in a comprehensive screening and treatment program (Figure 2). Young women should be aware of whether any direct relatives have a history of BC. They should also conduct self-examinations of both breasts for any lumps, nodules, skin changes resembling orange peel, or nipple discharge and retraction. In addition, young women should complete BC screenings regularly and on schedule. For those with a family history of BC, it is advisable to undergo genetic testing to determine whether they carry PVs in the BRCA1/2 genes. If young BC is diagnosed, the patient's prognosis and the risk of SPC should be estimated based on the molecular subtype of the BC and the type of PVs. Clinicians should explain the benefits and risks of treatment to patients. For surgical options, it is important to be vigilant about the risk of SPC occurring 10–15 years later. For HR+ patients, it is essential to closely monitor and actively prevent the development of endometrial cancer while undergoing ET. RT carries a high risk for the occurrence of SPC in the chest, and patients should be fully informed about the dual nature of these treatments. Young women can also take relevant intervention measures to reduce the occurrence of high-risk factors. For example, it is advisable to have the first pregnancy between the ages of 25 and 30. In addition, maintaining regular menstrual cycles and a healthy body weight, providing self-encouragement and stress reduction, and avoiding harmful habits such as smoking and drinking are all important steps.

Of course, the above represents an ideal situation, and many current studies still cannot fully explain the underlying mechanisms. First, the mechanisms leading to precancerous and tumor phenotypes are still unclear, and the changes in cancer tissue or the surrounding stromal components remain unknown. This makes it difficult to identify causal signals and their targets. For example, what causes the development of the TNBC, and whether pathogenic genetic mutations have corresponding therapeutic targets. Second, the field of BCYW still lacks strong predictive biomarkers and risk assessment screening tools. Factors related to BC, such as age, hormone levels, menstrual cycles, menopausal status, pregnancy, number of pregnancies, and BF, need to be evaluated as potential independent predictors of SPC in young BC survivors. Therefore, more predictive models are needed for further validation. Third, to better understand the risk of SPC in BCYW and the potential cellular basis, it is essential to describe the details of the hormonal interactions and feedback regulation between the breast and its stroma, as well as the hypothalamic–pituitary–gonadal axis. In addition, we need to explore how these signals affect breast development and the occurrence of SPC during cyclical reproduction. Thus, a comprehensive understanding and research into the occurrence of SPC in BCYW is necessary and aligns with current research trends.

In summary, this review emphasizes the occurrence of SPC, particularly among young BC

survivors. Consequently, regular monitoring and screening, along with appropriate treatment plans that weigh the benefits and risks, are crucial for BC survivors to enable early detection and intervention of potential SPC.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human or animal participants. Consent to participate: not applicable.

Consent for publication

Not applicable.

Author contributions

Xinyi Liang: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Yiwei Qin: Investigation; Writing – review & editing.

Pengwei Li: Investigation; Writing – review & editing.

You Mo: Conceptualization; Formal analysis; Supervision; Writing – review & editing.

Dawei Chen: Conceptualization; Funding acquisition; Project administration; Supervision; Validation; Writing – review & editing.

Acknowledgements

None.

Funding

This work was funded by the National Natural Science Foundation of China (82172676, 82373217), the Natural Science Foundation of Shandong (ZR2024JQ032), Shandong Natural Science Foundation Major Basic Research Project (ZR2023ZD26), Project supported by the State Key Program of National Natural Science of China (82030082).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

No datasets were generated or analyzed during the current study. Further inquiries can be directed to the corresponding author.

ORCID iDs

Xinyi Liang https://orcid.org/0009-0004-6610-1207

Yiwei Qin https://orcid.org/0009-0001-1871-4699

Pengwei Li https://orcid.org/0009-0003-4037-8569

You Mo https://orcid.org/0000-0001-5283-0741

Dawei Chen https://orcid.org/0000-0002-6762-7997

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209–249.
2. Bodmer A, Feller A, Bordoni A, et al. Breast cancer in younger women in Switzerland 1996-2009: a longitudinal population-based study. *Breast* 2015; 24: 112–117.
3. Merlo DF, Ceppi M, Filiberti R, et al. Breast cancer incidence trends in European women aged 20–39 years at diagnosis. *Breast Cancer Res Treat* 2012; 134: 363–370.
4. Molina-Montes E, Requena M, Sánchez-Cantalejo E, et al. Risk of second cancers cancer after a first primary breast cancer: a systematic review and meta-analysis. *Gynecol Oncol* 2015; 136: 158–171.
5. Arnold M, Morgan ME, Rumgay H, et al. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast* 2022; 66: 15–23.
6. Sung H, Freedman RA, Siegel RL, et al. Risks of subsequent primary cancers among breast cancer survivors according to hormone receptor status. *Cancer* 2021; 127: 3310–3324.
7. Copson E, Eccles B, Maishman T, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study. *J Natl Cancer Inst* 2013; 105: 978–988.
8. Yeo W, Lee HM, Chan A, et al. Risk factors and natural history of breast cancer in younger Chinese women. *World J Clin Oncol* 2014; 5: 1097–1106.
9. Raymond JS and Hogue CJR. Multiple primary tumours in women following breast cancer, 1973–2000. *Br J Cancer* 2006; 94: 1745–1750.

10. Ricceri F, Fasanelli F, Giraudo MT, et al. Risk of second primary malignancies in women with breast cancer: results from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 2015; 137: 940–948.

11. Rosenberg PS, Barker KA and Anderson WF. Estrogen receptor status and the future burden of invasive and in situ breast cancers in the United States. *J Natl Cancer Inst* 2015; 107: 20150610.

12. Soerjomataram I, Louwman WJ, de Vries E, et al. Primary malignancy after primary female breast cancer in the South of the Netherlands, 1972-2001. *Breast Cancer Res Treat* 2005; 93: 91–95.

13. Yu GP, Schantz SP, Neugut AI, et al. Incidences and trends of second cancers in female breast cancer patients: a fixed inception cohort-based analysis (United States). *Cancer Causes Control* 2006; 17: 411–420.

14. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; 69: 363–385.

15. Corso G, Veronesi P, Santomauro GI, et al. Multiple primary non-breast tumors in breast cancer survivors. *J Cancer Res Clin Oncol* 2018; 144: 979–986.

16. Li Z, Wu Q, Song J, et al. Risk of Second primary female genital malignancies in women with breast cancer: a SEER analysis. *Horm Cancer* 2018; 9: 197–204.

17. Graber-Naidich A, Choi E, Wu JT, et al. Smoking and the risk of second primary lung cancer among breast cancer survivors from the population-based UK biobank study. *Clin Lung Cancer* 2024; 25: 705–711.e7.

18. Chen F, Park SL, Wilkens LR, et al. Genetic risk of second primary cancer in breast cancer survivors: the multiethnic cohort study. *Cancer Res* 2022; 82(18): 3201–3208.

19. Schonfeld SJ, Morton LM, Berrington de González A, et al. Risk of second primary papillary thyroid cancer among adult cancer survivors in the United States, 2000-2015. *Cancer Epidemiology* 2020; 64: 101664.

20. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin* 2022; 72: 409–436.

21. Dong C and Chen L. Second malignancies after breast cancer: the impact of adjuvant therapy. *Mol Clin Oncol* 2014; 2: 331–336.

22. Yadav S, Boddicker NJ, Na J, et al. Contralateral breast cancer risk among carriers of germline pathogenic variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2. *J Clin Oncol* 2023; 41: 1703–1713.

23. Sun J, Chu F, Pan J, et al. BRCA-CRisk: a contralateral breast cancer risk prediction model for BRCA carriers. *J Clin Oncol* 2023; 41: 991–999.

24. Ellington TD, Miller JW, Henley SJ, et al. Trends in breast cancer incidence, by race, ethnicity, and age among women aged ⩾20 years – United States, 1999-2018. *MMWR Morb Mortal Wkly Rep* 2022; 71(2): 43–47.

25. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; 30(8): 1194–1220.

26. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). *Ann Oncol* 2022; 33: 1097–1118.

27. DeSantis CE, Ma J and Jemal A. Trends in stage at diagnosis for young breast cancer patients in the United States. *Breast Cancer Res Treat* 2019; 173: 743–747.

28. Wang X, Xia C, Wang Y, et al. Landscape of young breast cancer under 35 years in China over the past decades: a multicentre retrospective cohort study (YBCC-Catts study). *EClinicalMedicine* 2023; 64: 102243.

29. Hassaine Y, Jacquet E, Seigneurin A, et al. Evolution of breast cancer incidence in young women in a French registry from 1990 to 2018: Towards a change in screening strategy? *Breast Cancer Res* 2022; 24: 87.

30. Fazel A, Hasanpour-Heidari S, Salamat F, et al. Marked increase in breast cancer incidence in young women: a 10-year study from Northern Iran, 2004-2013. *Cancer Epidemiol* 2019; 62: 101573.

31. Sadjadi A, Nouraie M, Ghorbani A, et al. Epidemiology of breast cancer in the Islamic Republic of Iran: first results from a population-based cancer registry. *East Mediterr Health J* 2009; 15: 1426–1431.

32. Joko-Fru WY, Jedy-Agba E, Korir A, et al. The evolving epidemic of breast cancer in sub-Saharan Africa: results from the African Cancer Registry Network. *Int J Cancer* 2020; 147: 2131–2141.

33. Spronk I, Schellevis FG, Burgers JS, et al. Incidence of isolated local breast cancer recurrence and contralateral breast cancer: a systematic review. *Breast* 2018; 39: 70–79.

34. Chen LJ, Chang YJ and Chang YJ. Treatment and long-term outcome of breast cancer in very

young women: nationwide population-based study. *BJS Open* 2021; 5.

35. Alvarez-Bañuelos MT, Segura-Jaramillo KA, Gómez-Rivera EdC, et al. Age under 30 years as a predictor of poor survival in a cohort of Mexican women with breast cancer. *Cancer Control* 2021; 28: 10732748211047408.
36. Schaffar R, Bouchardy C, Chappuis PO, et al. A population-based cohort of young women diagnosed with breast cancer in Geneva, Switzerland. *PLoS One* 2019; 14: e0222136. 20190906.
37. Zeng Y, Wang J, Zhong X, et al. The disparities in prognostic prediction and annualized hazard function in different molecular subtypes between young Chinese and White American women with breast cancer. *Front Oncol* 2023; 13: 1199492. 20230710.
38. Billena C, Wilgucki M, Flynn J, et al. 10-Year Breast Cancer Outcomes in Women </=35 years of age. *Int J Radiat Oncol Biol Phys* 2021; 109: 1007–1018.
39. Schettini F, Blondeaux E, Molinelli C, et al. Characterization of HER2-low breast cancer in young women with germline BRCA1/2 pathogenetic variants: results of a large international retrospective cohort study. *Cancer* 2024; 130: 2746–2762.
40. Arecco L, Bruzzone M, Bas R, et al. Impact of hormone receptor status and tumor subtypes of breast cancer in young BRCA carriers. *Ann Oncol* 2024; 35: 792–804.
41. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol* 2018; 19: 169–180.
42. Malone KE, Darling JR, Neal C, et al. Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. *Cancer* 2000; 88(6): 1393–1402.
43. Luen SJ, Viale G, Nik-Zainal S, et al. Genomic characterisation of hormone receptor-positive breast cancer arising in very young women. *Ann Oncol* 2023; 34: 397–409.
44. Nash R, Goodman M, Lin CC, et al. State variation in the receipt of a contralateral prophylactic mastectomy among women who received a diagnosis of invasive unilateral early-stage breast cancer in the United States, 2004-2012. *JAMA Surg* 2017; 152: 648–657.
45. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687–1717.
46. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; 378: 1707–1716.
47. Leung TH, El Helali A, Wang X, et al. Trends and age, sex, and race disparities in time to second primary cancer from 1990 to 2019. *Cancer Med* 2023; 12: 22316–22324.
48. Brandt C, Vo JB, Gierach GL, et al. Second primary cancer risks according to race and ethnicity among U.S. breast cancer survivors. *Int J Cancer* 2024; 155: 996–1006.
49. Degeneffe A, De Maertelaer V, De Witte O, et al. The association between meningioma and breast cancer. *JAMA Network Open* 2023; 6: e2318620.
50. Lee KD, Chen SC, Chan CH, et al. Increased risk for second primary malignancies in women with breast cancer diagnosed at young age: a population-based study in Taiwan. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 2647–2655.
51. Goncalves E, Fontes F, Rodrigues JR, et al. Second primary cancers among females with a first primary breast cancer: a population-based study in Northern Portugal. *Breast Cancer Res Treat* 2024; 204: 367–376.
52. Kim H, Kim SS, Lee JS, et al. Epidemiology of second non-breast primary cancers among survivors of breast cancer: a Korean population-based study by the SMARTSHIP Group. *Cancer Res Treat* 2023; 55: 580–591.
53. Zhang BX, Brantley KD, Rosenberg SM, et al. Second primary non-breast cancers in young breast cancer survivors. *Breast Cancer Res Treat* 2024; 207: 587–597.
54. Kim H, Yoon TI, Kim S, et al. Age-related incidence and peak occurrence of contralateral breast cancer. *JAMA Netw Open* 2023; 6: e2347511.
55. Li D, Weng S, Zhong C, et al. Risk of second primary cancers among long-term survivors of breast cancer. *Front Oncol* 2019; 9: 1426.
56. Allen I, Hassan H, Joko-Fru WY, et al. Risks of second primary cancers among 584,965 female and male breast cancer survivors in England: a 25-year retrospective cohort study. *Lancet Reg Health Eur* 2024; 40: 100903.
57. Yuan L, Chen Y, Li X, et al. Predictive models for overall survival in breast cancer patients with

a second primary malignancy: a real-world study in Shanghai, China. *BMC Womens Health* 2022; 22: 498.

58. Molina-Montes E, Perez-Nevot B, Pollan M, et al. Cumulative risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer: a systematic review and meta-analysis. *Breast* 2014; 23: 721–742.
59. Su L, Xu Y, Ouyang T, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers in a large cohort of unselected Chinese breast cancer patients. *Int J Cancer* 2020; 146: 3335–3342.
60. Brantley KD, Rosenberg SM, Collins LC, et al. Second primary breast cancer in young breast cancer survivors. *JAMA Oncol* 2024; 10: 718–725.
61. Agarwal S, Pappas L, Matsen CB, et al. Second primary breast cancer after unilateral mastectomy alone or with contralateral prophylactic mastectomy. *Cancer Med* 2020; 9: 8043–8052.
62. Watt GP, John EM, Bandera EV, et al. Race, ethnicity and risk of second primary contralateral breast cancer in the United States. *Int J Cancer* 2021; 148: 2748–2758.
63. Burt LM, Ying J, Poppe MM, et al. Risk of secondary malignancies after radiation therapy for breast cancer: Comprehensive results. *Breast* 2017; 35: 122–129.
64. Berrington de Gonzalez A, Curtis RE, Gilbert E, et al. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. *Br J Cancer* 2010; 102: 220–226.
65. Morton LM, Gilbert ES, Hall P, et al. Risk of treatment-related esophageal cancer among breast cancer survivors. *Ann Oncol* 2012; 23: 3081–3091.
66. Schaapveld M, Visser O, Louwman MJ, et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. *J Clin Oncol* 2008; 26: 1239–1246.
67. Reiner AS, Robson ME, Mellemkjaer L, et al. Radiation Treatment, ATM, BRCA1/2, and CHEK2*1100delC pathogenic variants and risk of contralateral breast cancer. *J Natl Cancer Inst* 2020; 112: 1275–1279.
68. Wei JL, Jiang YZ and Shao ZM. Survival and chemotherapy-related risk of second primary malignancy in breast cancer patients: a SEER-based study. *Int J Clin Oncol* 2019; 24: 934–940.
69. Shoemaker ML, White MC, Wu M, et al. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013. *Breast Cancer Res Treat* 2018; 169: 595–606.
70. Song Y, Wang J, Wang X, et al. Characteristics and survival analysis of breast cancer survivors with metachronous double primary cancers: a retrospective cohort study. *Transl Cancer Res* 2023; 12: 939–948.
71. Miller KD, Fidler-Benaoudia M, Keegan TH, et al. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin* 2020; 70: 443–459.
72. Guzman-Arocho YD, Rosenberg SM, Garber JE, et al. Clinicopathological features and BRCA1 and BRCA2 mutation status in a prospective cohort of young women with breast cancer. *Br J Cancer* 2022; 126: 302–309.
73. Azim HA Jr and Partridge A. Biology of breast cancer in young women. *Breast Cancer Res* 2014; 16(4): 427.
74. Freedman RA, Virgo KS, Labadie J, et al. Receipt of locoregional therapy among young women with breast cancer. *Breast Cancer Res Treat* 2012; 135: 893–906.
75. Dominici L, Hu J, Zheng Y, et al. Association of local therapy with quality-of-life outcomes in young women with breast cancer. *JAMA Surgery* 2021; 156.
76. Tesch ME, Zheng Y, Rosenberg SM, et al. Estrogen levels in young women with hormone receptor-positive breast cancer on ovarian function suppression therapy. *NPJ Breast Cancer* 2024; 10: 67.
77. Baek SY, Noh WC, Ahn SH, et al. Adding ovarian suppression to tamoxifen for premenopausal women with hormone receptor-positive breast cancer after chemotherapy: an 8-year follow-up of the ASTRRA Trial. *J Clin Oncol* 2023; 41: 4864–4871.
78. Kim HA, Lee JW, Nam SJ, et al. Adding ovarian suppression to tamoxifen for premenopausal breast cancer: a randomized phase iii trial. *J Clin Oncol* 2020; 38: 434–443.
79. Pagani O, Walley BA, Fleming GF, et al. Adjuvant Exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-up of the combined TEXT and SOFT trials. *J Clin Oncol* 2023; 41: 1376–1382.
80. Lønning PE. Aromatase inhibitors in breast cancer. *Endocr Relat Cancer* 2004; 11(2): 179–189.
81. Ingle JN, Cairns J, Suman VJ, et al. Anastrozole has an association between

degree of estrogen suppression and outcomes in early breast cancer and is a ligand for estrogen receptor alpha. *Clin Cancer Res* 2020; 26: 2986–2996.

82. Andersson M, Jensen MB, Engholm G, et al. 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: 755–764.
83. Nordenskjöld A, Fohlin H, Rosell J, et al. Breast cancer survival and incidence of second primary cancers after 30 years in a randomized study of two versus five years of adjuvant tamoxifen therapy. *Breast* 2023; 71: 63–68.
84. Zhou J, Lin Z, Lyu M, et al. Prognostic value of lymph node ratio in non-small-cell lung cancer: a meta-analysis. *Jpn J Clin Oncol* 2020; 50: 44–57.
85. Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol* 2010; 28: 2874–2880.
86. Kirova YM, De Rycke Y, Gambotti L, et al. Second malignancies after breast cancer: the impact of different treatment modalities. *Brit J Cancer* 2008; 98: 870–874.
87. Li W, Xiao H, Xu X, et al. The impact of radiotherapy on the incidence of secondary malignancies: a pan-cancer study in the US SEER cancer registries. *Curr Oncol* 2021; 28: 301–316.
88. Liu J, Jiang W, Mao K, et al. Elevated risks of subsequent endometrial cancer development among breast cancer survivors with different hormone receptor status: a SEER analysis. *Breast Cancer Res Treat* 2015; 150: 439–445.
89. Li C, Lyu Z, Wang Z, et al. The changes of subtype markers between first and second primary breast cancers. *Cancer Med* 2023; 12: 13649–13660.
90. Kramer I, Schaapveld M, Oldenburg HSA, et al. The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. *J Natl Cancer Inst* 2019; 111: 709–718.
91. Walbaum B, Garcia-Fructuoso I, Martinez-Saez O, et al. Hormone receptor-positive early breast cancer in young women: a comprehensive review. *Cancer Treat Rev* 2024; 129: 102804.
92. Lyons TR, Schedin PJ and Borges VF. Pregnancy and breast cancer: when they collide. *J Mammary Gland Biol Neoplasia* 2009; 14: 87–98.
93. Nichols HB, Schoemaker MJ, Cai J, et al. Breast cancer risk after recent childbirth: a pooled analysis of 15 prospective studies. *Ann Intern Med* 2019; 170: 22–30.
94. Jung AY, Ahearn TU, Behrens S, et al. Distinct reproductive risk profiles for intrinsic-like breast cancer subtypes: pooled analysis of population-based studies. *J Natl Cancer Inst* 2022; 114: 1706–1719.
95. Zhang Z, Ye S, Bernhardt SM, et al. Postpartum breast cancer and survival in women with germline BRCA pathogenic variants. *JAMA Netw Open* 2024; 7: e247421.
96. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012; 13: 1141–1151.
97. Fu J, Wu L, Fu W, et al. How young is too young in breast cancer? Young breast cancer is not a unique biological subtype. *Clin Breast Cancer* 2018; 18: e25–e39.
98. Menen RS and Hunt KK. Considerations for the treatment of young patients with breast cancer. *Breast J* 2016; 22: 667–672.
99. Wang S, Wang YX, Sandoval-Insausti H, et al. Menstrual cycle characteristics and incident cancer: a prospective cohort study. *Hum Reprod* 2022; 37: 341–351.