

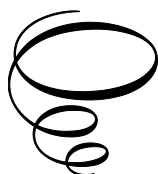
Second Primary Cancers in Cancer Survivors

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Edited by

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CONTENTS

Introduction	1
<i>Reza Alizadeh-Navaei, Akbar Hedayatizadeh-Omran and Mahmood Moosazadeh</i>	
Second Primary Cancers in Breast Cancer Survivors.....	9
<i>Seyedeh Mahta Moradi and Ghasem Janbabaei</i>	
Second Primary Cancers in Colorectal Cancer Survivors	23
<i>Shamim Khorshidian and Iradj Maleki</i>	
Second Primary Cancers in Prostate Cancer Survivors	37
<i>Mohammad Moein Maddah and Ahmad Deilami</i>	
Second Primary Cancers in Head and Neck Cancers Survivors.....	66
<i>Alireza Razavi and Maryam Alizadeh Forutan</i>	
Second Primary Malignancies in Thyroid Cancer	79
<i>Mobina Gheibi, Mohamadreza Dehghannezhad and Adeleh Bahar</i>	
Second Primary Cancers in Non-Hodgkin Lymphoma Survivors.....	91
<i>Erfan Ghadirzadeh and Leila Mirzakhani</i>	
Second Primary Cancers in Hodgkin Lymphoma Survivors	106
<i>Marzieh Bathai and Mohammad Eslami Jouybari</i>	
Second Primary Cancers in Leukemia Survivors	121
<i>Parisa Maleki Dana and Mohammad Naderisorki</i>	
Second Primary Cancers in Bladder Cancer Survivors	136
<i>Safieh Ebrahimi and Ehsan Zaboli</i>	
Second Primary Cancers in Cervical Cancer Survivors.....	164
<i>Mobina Gheibi and Aghdas Ebadi Jamkhaneh</i>	

Second Primary Cancers in Ovary Cancer Survivors	181
<i>Amirhossein Hessami and Ramin Shekarriz</i>	
Second Primary Cancers in Kidney Cancer Survivors	188
<i>Fatemeh Sadoughi and Maryam Montazeri</i>	
Second Primary Cancers in Multiple Myeloma Survivors	199
<i>Seyedeh-Kiana Razavi-Amoli, Amin Ghanbari and Zohreh Ehsani</i>	
Index	214

INTRODUCTION

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1. Introduction

In 2022, global cancer statistics reported nearly 20 million new cases including nonmelanoma skin cancers and 9.7 million deaths, with roughly 1 in 5 people developing cancer in their lifetime and 1 in 9 men and 1 in 12 women dying from it. Lung cancer was the most commonly diagnosed (12.4% of cases) and deadliest (18.7% of deaths), followed by female breast, colorectal, prostate, and stomach cancers. Incidence rates varied significantly by region, with the highest in Australia/New Zealand (~500 per 100,000 men, ~400 per 100,000 women) and the lowest in Western Africa (<100 per 100,000 men) and South-Central Asia (~100 per 100,000 women) (Bray et al. 2024). In the U.S., cancer mortality has declined since 1991, preventing 4.5 million deaths due to reduced smoking, earlier detection, and better treatments. Incidence rates have fallen in men but risen in women, narrowing the gender gap from 1.6 in 1992 to 1.1 in 2021. Despite progress, disparities persist, with growing risks among younger adults, particularly women (Siegel et al. 2025). However, these advances contrast with global trends, where cancer remains a rising threat. The increasing burden undermines development, prompting initiatives like the

WHO's Global Action Plan on Non-Communicable Diseases and the Sustainable Development Goals (Fitzmaurice et al. 2018). While cancer mortality rates are steadily decreasing, new case rates have stabilized in men and shown a slight rise in women. These shifts stem from evolving risk factors, variations in screening uptake, advancements in diagnostic methods, and improved treatments. Early detection remains critical, as many cancers are preventable or highly treatable when caught at an initial stage (Santucci et al. 2020).

Against, second primary cancers are new, distinct malignancies that arise in individuals who have previously had cancer. According to population-based research, the likelihood of developing a second primary cancers is 10–60% higher compared to the general population (Oh 2017). Cancer survivors face an increased likelihood of developing a second primary cancer, which can result from various clinical factors, including previous treatments for the initial cancer like chemotherapy or radiation therapy (Heydari et al. 2021). Alkylating agents may also elevate the risk of developing a second primary cancer, such as lung, gastrointestinal, bladder, and breast cancers and sarcomas, particularly when used in combination with radiation therapy (Demoor-Goldschmidt and de Vathaire 2019). Second primary cancers caused by radiation usually have a longer latency period of at least 5 to 10 years following treatment and are linked to factors such as the cumulative dose, the area exposed, and the patient's age at the time of treatment (Dracham, Shankar, and Madan 2018). As well as, some newer interventions, such as hematopoietic stem cell transplantation, can increase the risk of developing second primary cancers (Heydari et al. 2020). Additionally, lifestyle habits such as smoking and obesity are associated with second primary cancers (Sung et al. 2020). About genetic factors, the main genes associated with second primary cancers include TP53, linked to Li-Fraumeni syndrome, which predisposes carriers to multiple malignancies; BRCA1 and BRCA2, which increase risks of contralateral breast cancer and other tumors in hereditary breast-ovarian cancer syndrome; PTEN, implicated in Cowden disease; MLH1, MSH2, and MSH6, DNA mismatch repair genes tied to hereditary nonpolyposis colorectal cancer; CHEK2, a multiorgan cancer susceptibility gene; FANCA-FANCL including FANCD1/BRCA2, part of the Fanconi anemia-BRCA pathway, which heightens sensitivity to DNA-damaging therapies; RB1, where germline mutations raise radiation-associated sarcoma risk; ATM, associated with radiation sensitivity in ataxia-telangiectasia; CDKN2A, related to melanoma risk; and Rad9, involved in DNA damage response. These genes contribute to second cancers through hereditary syndromes, treatment-related carcinogenesis such as

chemo/radiotherapy, and gene-environment interactions (Travis et al. 2006). Therefore, it seems that lifestyle interventions such as smoking cessation, alcohol counseling, maintaining a healthy diet, and engaging in physical activity, along with cancer screening and genetic counseling can help decrease or prevent the risk of second primary cancers in cancer survivors (Cullinan et al. 2021; Demark-Wahnefried and Jones 2008).

In the case of cancer patients who have good prognosis, secondary cancer, rather than the original malignancy, often become the leading cause of mortality; for example, in breast cancer survivors, second primary cancer increases the risk of death by approximately 3–4 times (Oh 2017). So Screening for second primary cancers is crucial in cancer survivors. For female patients who received chest radiotherapy, annual mammography and breast MRI are recommended (Moskowitz et al. 2021; Saslow et al. 2007). Modeling studies indicate that early and regular breast cancer screening in high-risk survivors such as those with a history of childhood cancer, could reduce breast cancer mortality by 50% or more (Yeh et al. 2020). However, many at-risk patients still do not receive adequate screening (Yan et al. 2020). For survivors treated with abdominal, pelvic, spinal, or total body irradiation, colorectal cancer surveillance should be considered (Hampton et al. 2021). Additionally, lung cancer screening is advised for survivors of smoking-related cancers, such as oral/pharyngeal and bladder cancers (Sung et al. 2020). In pediatric, adolescent, and young adult survivors who underwent cranial radiotherapy, evidence supporting routine MRI surveillance for CNS tumors such as meningiomas remains limited. Instead, these patients should receive regular symptom-focused assessments include history and physical exams every 1–5 years (Bowers et al. 2021).

Preventive care plays a crucial role in cancer survivorship, with particular emphasis on diet, physical activity, smoking cessation, and comorbidity management. Maintaining a healthy diet and regular exercise can significantly enhance quality of life while mitigating disease- and treatment-related side effects. However, cancer survivors often exhibit lower physical activity levels than the general population, which may contribute to persistent fatigue, obesity, post-chemotherapy weight gain, and physical limitations (Cao, Friedenreich, and Yang 2022; Jiang et al. 2022). Tobacco use remains a critical concern, as survivors who continue smoking face a markedly elevated risk of subsequent cancers (Klosky et al. 2007; Mariotto et al. 2007). Despite this, 12–15% of survivors are current smokers (Underwood et al. 2012), underscoring the need for clinicians to routinely assess tobacco use and offer cessation support (U.S. Preventive

Services Task Force 2009). While alcohol's link to cancer recurrence remains understudied, limiting intake is advised to reduce the risk of new primary cancers (Doyle et al. 2006).

In this book, we provide a broad overview of second primary cancers that is arising in survivors of initial malignancies with high survival rates, exploring their epidemiology, risk factors, underlying mechanisms, prevention strategies, and clinical management.

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SECOND PRIMARY CANCERS IN BREAST CANCER SURVIVORS

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1. Epidemiology of breast cancer

Breast cancer has emerged as the most commonly diagnosed cancer globally, with an estimated 2.26 million new cases reported in 2020, making it the leading cause of cancer-related mortality among women worldwide (Wilkinson and Gathani 2022). The global distribution of breast cancer incidence is closely linked to levels of human development. Rapidly industrializing and economically transforming regions are experiencing a significant rise in cases, reflecting the complex interaction between socioeconomic factors and disease burden. Over the past three decades, both the incidence and mortality of breast cancer have increased, a trend attributed to shifting risk factor profiles, enhanced cancer registration systems, and improved detection methods (Łukasiewicz et al. 2021).

There are pronounced geographic disparities in breast cancer incidence and mortality rates across different regions of the world. Age-standardized incidence rates exhibit considerable variation, with Belgium reporting the highest rate at 112.3 cases per 100,000 population, while Iran shows the lowest incidence at 35.8 cases per 100,000. This wide range highlights significant differences in disease burden among populations. Similarly, age-standardized mortality rates also vary substantially; Fiji has the highest reported mortality rate at 41.0 deaths per 100,000 population, in contrast to

South Korea, which records the lowest mortality rate of 6.4 deaths per 100,000. These disparities may reflect differences in healthcare infrastructure, screening practices, and treatment availability across countries. An additional noteworthy observation is the variation in the peak age at breast cancer diagnosis between populations. In numerous Asian and African nations, the age at which breast cancer is most frequently diagnosed occurs more than ten years earlier than that seen in European and North American populations. This marked difference in peak diagnosis age may be attributed to a complex interplay of factors, including genetic predispositions, environmental exposures, lifestyle differences, and variations in healthcare access and early detection programs. Understanding these underlying causes is crucial for developing targeted prevention and intervention strategies tailored to the specific needs of diverse populations worldwide (Lei et al. 2021). From 2012 to 2021, the incidence of breast cancer exhibited a consistent annual increase of approximately 1%, predominantly among patients diagnosed at a localized stage and with hormone receptor-positive tumors. This upward trend was particularly pronounced in women under the age of 50, who experienced an average annual increase of 1.4%, compared to a 0.7% increase among older women. The most notable increases were observed among Asian American and Pacific Islander women, who demonstrated the highest growth rates in both younger (2.7%) and older (2.5%) age cohorts. Consequently, although young Asian American and Pacific Islander women had the second lowest breast cancer incidence rate in 2000 (57.4 per 100,000), by 2021, their incidence rate had risen to the highest level (86.3 per 100,000), closely approaching that of White women (86.4 per 100,000) and exceeding that of Black women (81.5 per 100,000) (Giaquinto et al. 2024). The etiology of breast cancer involves a combination of modifiable and non-modifiable risk factors. Modifiable risk factors include body weight, use of hormone replacement therapy, and reproductive history. Non-modifiable factors, on the other hand, encompass age at menarche and menopause, breast density, and a family history of the disease. Genetic predisposition plays a substantial role; twin studies suggest that hereditary factors account for approximately 30% of breast cancer cases. Women with at least one first-degree relative diagnosed with breast cancer have about twice the risk of developing the disease. Furthermore, around 5–10% of cases follow a Mendelian inheritance pattern, indicating a strong hereditary component (McVeigh, Tepper, and McVeigh 2021). The age-standardized incidence rates of breast cancer by country from the global burden of disease study was presented in Figure 1.

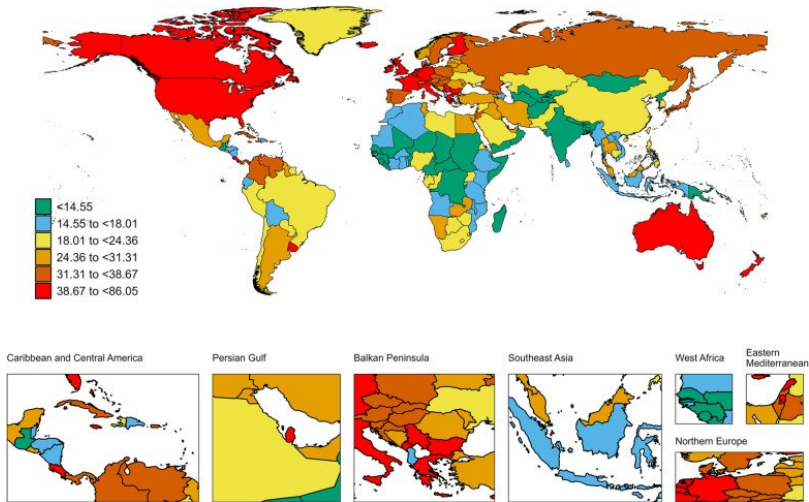


Figure 1. Age-standardized incidence rates of breast cancer by country from the global burden of disease study 2021 (Sha et al. 2024)

2. Breast cancer survival

Breast cancer (BC) remains the foremost cause of cancer-related mortality among women worldwide, posing a significant public health challenge in 2008 alone, developing countries accounted for approximately 1.38 million new breast cancer diagnoses, representing nearly 50% of global breast cancer cases and contributing to 60% of the associated mortality. These statistics underscore the pronounced global disparities in breast cancer burden and outcomes. Survival rates vary markedly between developed and developing regions, with a 5-year survival rate estimated at 80% in developed countries but less than 40% in developing nations. This discrepancy reflects differences in healthcare infrastructure, access to screening and early diagnosis, and availability of advanced treatment modalities (Ning et al. 2020). Since the mid-1970s, advances in breast cancer screening and treatment have substantially reduced mortality rates. By 2019, breast cancer mortality in women had declined by approximately 58%, from a hypothetical 64 deaths per 100,000 women without intervention to 27 deaths per 100,000, age-adjusted. This improvement is attributable to multiple factors: treatment of metastatic disease accounts for around 29% of the mortality reduction, screening programs contribute 25%, and treatment of early-stage (I to III) breast cancer explains 47% of

the decline. These findings emphasize the critical importance of early detection and comprehensive management in improving patient outcomes (Caswell-Jin et al. 2024). Extensive research has identified numerous prognostic factors influencing breast cancer survival. Key determinants include patient age, ethnicity, tumor characteristics such as histological type and size, lymph node involvement, disease stage at diagnosis, hormone receptor (HR) status, and human epidermal growth factor receptor-2 (HER2) expression (Tan et al. 2021). For example, hormone receptor-positive (HR+) tumors, particularly those that are HER2-negative, generally exhibit more favorable prognoses compared to HER2-positive or triple-negative breast cancer subtypes. Specifically, four-year survival rates for HR+/HER2- patients reach approximately 92.5%, followed by 90.3% for HR+/HER2+, 82.7% for HR-/HER2+, and the poorest survival of 77.0% observed in the triple-negative subtype. These subtype-specific survival differences guide tailored therapeutic strategies and highlight the necessity for subtype-specific research (Howlander et al. 2018).

Additional patient-specific factors also correlate strongly with survival outcomes. A study conducted in 2022 identified that advanced age, late-stage disease (stages III and IV), comorbid conditions such as anemia and diabetes, treatment limited to chemotherapy alone, metastatic disease, blood type AB, positive family history of breast cancer, and cancer recurrence were associated with higher mortality rates. These factors cumulatively influence survival times, indicating the complex interplay between biological, clinical, and genetic factors in breast cancer prognosis (Feleke, Tesfaw, and Mitku 2022). Stage at diagnosis remains one of the most critical predictors of survival. Five-year overall survival rates demonstrate a steep decline with advancing stage: 94.4% for stage I, 85.0% for stage II, 56.6% for stage III, and a dramatic reduction to 28.3% for stage IV disease (Chitapanarux et al. 2019). These statistics highlight the essential role of early diagnosis and intervention. Moreover, disparities in survival extend beyond stage and subtype to demographic factors such as age and ethnicity. Younger (<40 years) and older (>70 years) patients tend to have less favorable survival outcomes compared to those diagnosed between 40 and 69 years of age. Although survival has improved significantly over time for most age groups, improvements are less marked among patients diagnosed after age 70 (Nordenskjöld et al. 2019).

Ethnic disparities in breast cancer survival remain a significant concern. Five-year overall survival rates demonstrate considerable variation across racial and ethnic groups, with rates reported at 85.0% among non-Hispanic Whites, 84.8% among Hispanic Whites, 79.4% among Hispanic Blacks,

and 72.7% among non-Hispanic Blacks. Importantly, non-Hispanic Black (NHB) women experience a statistically significant decrease in overall survival relative to other groups, even after controlling for socioeconomic status and clinical factors. This is evidenced by a hazard ratio of 1.25 (95% confidence interval: 1.01–1.52), indicating a 25% higher risk of mortality. These persistent disparities underscore the need for continued research and targeted interventions to address the underlying causes (Goel et al. 2021).

Treatment timing and adherence to guideline-recommended intervals between diagnosis and various treatment modalities also impact survival. Delays exceeding recommended time frames between diagnosis and surgery, surgery and chemotherapy, or chemotherapy and radiotherapy are associated with poorer breast cancer-specific survival. These results underscore the importance of optimizing care pathways and minimizing treatment delays to improve outcomes (Kou et al. 2023). These results underscore the importance of optimizing care pathways and minimizing treatment delays to improve outcomes. The evolution of breast cancer treatment has seen the introduction of multimodality approaches, including surgery, chemotherapy, radiotherapy, and targeted therapies. Novel therapeutics, particularly anti-HER2 targeted agents such as trastuzumab, have revolutionized the management of HER2-positive breast cancer and contributed substantially to improved survival rates. These therapies exemplify precision medicine's promise in oncology, offering more effective and less toxic treatment options tailored to tumor biology (Amato, Guarneri, and Girardi 2023).

Beyond clinical and molecular factors, lifestyle and comorbid conditions also influence breast cancer outcomes. Healthy dietary patterns have been associated with a reduced risk of breast cancer and lower all-cause mortality among breast cancer patients (Hou et al. 2019). This aligns with growing evidence supporting the role of modifiable risk factors in cancer prognosis and survivorship. Additionally, comorbidities such as diabetes and anemia negatively impact survival, highlighting the need for comprehensive care addressing overall health status (Feleke, Tesfaw, and Mitku 2022). The age-standardized deaths rates of breast cancer by country from the global burden of disease study was presented in Figure 2.

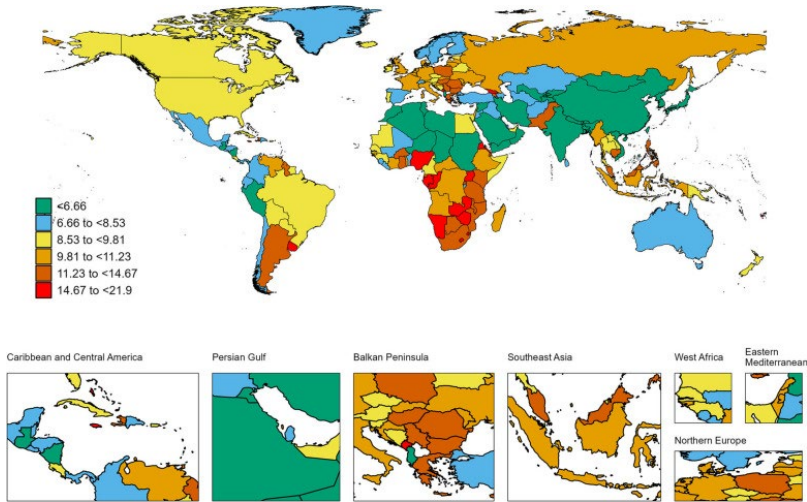


Figure 2. Age-standardized deaths rates of breast cancer by country from the global burden of disease study 2021 (Sha et al. 2024)

3. Secondary malignancy after breast cancer

Improvements in breast cancer (BC) screening and treatment have undoubtedly enhanced survival rates; however, they have also unveiled a concerning long-term consequence: a heightened risk of developing a second primary malignancy (SPM) in survivors when compared to the general population. This pattern reveals the complex interplay between therapeutic interventions, genetic predisposition, and tissue-specific carcinogenic pathways (Chen et al. 2024). A key driver of these elevated risks is treatment-related: breast irradiation, adjuvant chemotherapy, and tamoxifen therapy are implicated in the development of secondary cancers, occasionally surfacing decades after initial therapy (Matesich and Shapiro 2003). Longitudinal registry data elucidate this relationship, demonstrating that the cumulative incidence of second primary malignancies (SPM) was approximately 3.6% within five years of breast cancer diagnosis, increasing to 8.2% at ten years, and reaching 13.9% by fifteen years. The standardized incidence ratio (SIR) for all non-breast primary cancers was 1.26 (95% confidence interval [CI], 1.23–1.30), with significantly elevated risks observed for colorectal, uterine, lung, ovarian, and thyroid cancers, as well as leukemia. These associations persisted even after excluding cancers diagnosed within the first six months following the initial diagnosis;

however, the increased risks for leukemia and colorectal cancer were no longer statistically significant (Silverman, Lipshitz, and Keinan-Boker 2017). Notably, molecular subtype and family history also play substantial roles. Among BC survivors, ER/PR-positive tumors are disproportionately represented among those who develop SPMs, especially in individuals under age 50 with a family history of malignancy. Interestingly, the incidence of SPM was similar whether individuals received chemotherapy, radiation, both, or neither (Chen et al. 2024). A critical example of therapy-related SPM is secondary hematologic malignancy, particularly therapy-induced acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). These treatment-associated leukemias are becoming increasingly prominent and carry a dire prognosis (Arslan et al. 2011). Evidence is most robust with alkylating agents: high-risk agents such as melphalan have shown up to a tenfold greater leukemogenic potential than cyclophosphamide. Standard-dose cyclophosphamide carries a risk of <0.5% for AML/MDS after 8–10 years, although higher dosing regimens notably elevate this risk. Topoisomerase II inhibitors (e.g., etoposide, mitoxantrone) contribute significantly to AML development, with mitoxantrone presenting a higher leukemogenic potential than anthracyclines. In contrast, taxanes have not demonstrated a statistically significant link to secondary leukemia in major clinical trials. The role of granulocyte colony-stimulating factor (G-CSF) remains ambiguous: some analysis suggest increased leukemia risk, whereas others show no association. Overall, higher cumulative chemotherapy dose and use of certain drug classes are central to secondary leukemia risk; hence, therapeutic regimens must balance efficacy with long-term safety. (Dong and Chen 2014) Recent evidence increasingly identifies ovarian cancer as a significant second primary malignancy (SPM) among breast cancer survivors, frequently diagnosed several years following the initial breast cancer diagnosis, often due to inadequate clinical surveillance. Lee et al. reported an incidence rate of secondary tumors of approximately 2.02% in breast cancer survivors, with ovarian cancer constituting 0.34% of these cases. Notably, young women with a history of breast cancer remain at an elevated risk for developing ovarian cancer for up to 20 years post-diagnosis. This association is likely driven by shared sex hormone regulatory mechanisms and genetic mutations, particularly in the context of Hereditary Breast and Ovarian Cancer Syndrome (HBOCS), which is estimated to account for 2–7% of breast cancer cases. From a clinical perspective, accurate differentiation between primary ovarian cancer and metastatic breast cancer involving the ovary is critical for guiding appropriate treatment strategies and informing prognosis (Liu et al. 2025).

Contralateral breast cancer (CBC) represents a clinically significant subtype of second primary malignancy. In a retrospective cohort study involving 5,003 women diagnosed with primary breast cancer (PBC) and treated between 2000 and 2020, 145 patients were subsequently diagnosed with CBC—defined as occurring at least six months following the initial diagnosis—while 4,858 remained PBC survivors. Among the CBC cases, 72.13% were estrogen receptor (ER)-positive, 66.67% progesterone receptor (PR)-positive, and 30.00% human epidermal growth factor receptor 2 (HER2)-positive. Invasive ductal carcinoma accounted for 69.57% of these tumors. Additionally, 81.90% of patients with CBC underwent adjuvant chemotherapy, and 83.64% received external radiotherapy. The median interval to CBC diagnosis was 3.92 years, with a five-year disease-free interval (DFI) following the initial breast cancer diagnosis of 97%. Multivariate analysis identified age ≥ 60 years as significantly associated with a reduced risk of developing CBC. Notably, family history was not a strong predictor in this cohort, as 69.57% of CBC cases had no reported familial breast cancer history. These findings provide valuable insights for developing personalized surveillance strategies for contralateral breast cancer (Avatefi et al. 2024).

A family history of breast cancer has also been associated with an increased risk of gynecologic second primary malignancies (SPMs). Ovarian and endometrial cancers are among the most common gynecologic SPMs observed, with an overall incidence of approximately 0.3%. Notably, approximately 75% of these malignancies develop within five years of the initial breast cancer diagnosis. However, late-onset cases, particularly endometrial cancer, have been documented up to 15 years post-diagnosis, underscoring the persistent nature of this risk. This elevated risk is strongly linked to tamoxifen therapy, typically prescribed for durations of five to ten years. Women treated with tamoxifen exhibit an approximately fourfold increased risk of endometrial cancer compared to untreated patients, corresponding to 50 excess cases per 10,000 women at ten years. Findings from early adjuvant clinical trials and observational studies support these observations, indicating that tamoxifen use is associated with a two- to threefold increase in the relative risk of developing endometrial cancer. Nevertheless, given tamoxifen's substantial survival benefits, the overall risk-benefit ratio remains favorable (Yadav et al. 2017).

4. Risk of secondary malignancies after breast cancer

Advancements in diagnostic and therapeutic modalities for breast cancer have significantly improved patient survival rates, consequently increasing the likelihood of developing subsequent primary malignancies. (Long, Wang, and Che 2021) Specific tumor characteristics, including poor differentiation, larger tumor size, and advanced nodal (N) stage, have been identified as significant risk factors for the development of second primary cancers (SPCs) in breast cancer survivors (Li et al. 2022). In a comprehensive cohort study comprising 409,796 first primary breast cancer patients, 18,283 individuals were diagnosed with at least one second primary malignancy (SPM). Notably, the standardized incidence ratio (SIR) for SPM following HER2-positive breast cancer was significantly lower compared to HER2-negative cases (SIR 1.03 vs. 1.13; relative risk [RR] 0.92; 95% confidence interval [CI], 0.88–0.96; $p < 0.001$) (Lin et al. 2021). The highest elevated risks were observed for leukemia (standardized incidence ratio [SIR] 2.07; 95% confidence interval [CI], 1.52–2.75), ovarian cancer (SIR 1.60; 95% CI, 1.27–2.04), and gynecological cancers—including cervical and endometrial malignancies (SIR 1.60; 95% CI, 1.34–1.89; $p < 0.0001$). Conversely, the risk of gastrointestinal cancers, despite being the most prevalent, was reduced (SIR 0.82; 95% CI, 0.70–0.95; $p < 0.007$). The increased incidence of leukemia was primarily associated with chemotherapy exposure, whereas hormone therapy was strongly correlated with elevated risks of gynecological cancers. Radiotherapy alone also contributed significantly, though to a lesser extent, to the incidence of both leukemia and gynecological malignancies. Furthermore, radiotherapy was implicated in increased risks of sarcomas and lung cancer. No statistically significant elevation in risk was identified for malignant melanoma, lymphoma, genitourinary, thyroid, or head and neck cancers (Kirova et al. 2008). Furthermore, breast cancer survivors who received radiation therapy exhibited an increased risk of secondary malignancies at specific anatomical sites compared to the general population; however, even those without radiation exposure demonstrated elevated risks (Burt et al. 2017). Given that radiotherapy carries a substantial risk for SPC development within the thoracic region, patients should be thoroughly counseled regarding the dual risks and benefits of such treatments (Liang et al. 2025). The risk of second malignancies generally diminishes with increasing age at exposure; data from atomic bomb survivor studies illustrate a decrease in risk from approximately 15% per sievert (Sv) for those exposed before age 10 to around 1% per Sv for individuals exposed after age 60 (Xie et al.

2018). Correspondingly, women diagnosed with breast cancer before age 50 face a higher excess risk of SPCs compared to those diagnosed at age 50 or older (SIR 1.77; 95% CI, 1.63–1.91 vs. 1.20; 95% CI, 1.15–1.24, respectively) (Silverman, Lipshitz, and Keinan-Boker 2017). The modifiable and non-modifiable risk factors for second primary cancer in breast cancer survivors shown in figure 3.

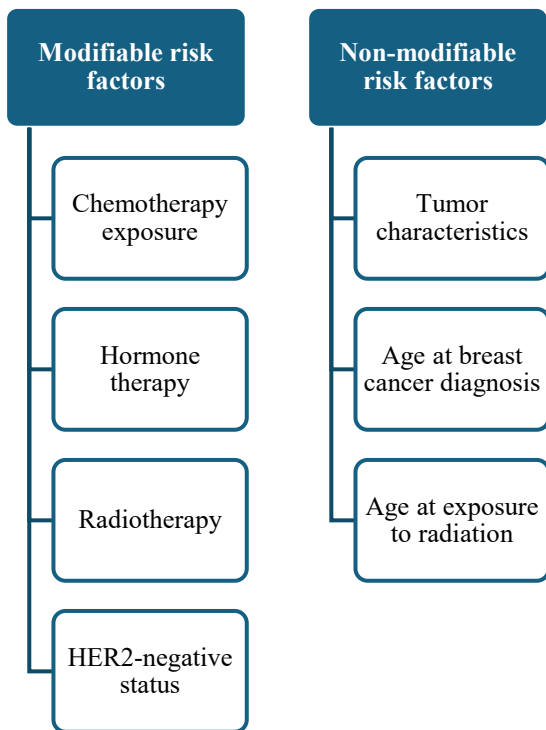


Figure 3: Risk factors for second primary cancer in breast cancer survivors

5. Management of secondary malignancies after breast cancer

The management of second primary cancers prioritizes early detection through routine screenings consistent with established guidelines for the general population, complemented by tailored interventions for individuals identified as high risk, including genetic counseling. Screening protocols for second primary malignancies encompass Pap smear and human

papillomavirus (HPV) DNA testing every three to five years for cervical cancer; fecal occult blood testing, stool DNA testing, flexible sigmoidoscopy, colonoscopy, or computed tomography (CT) colonography for colorectal cancer; patient education regarding abnormal bleeding during menopause for early detection of endometrial cancer; and annual low-dose CT scans for lung cancer screening in adults aged 55 to 74 years with a smoking history of at least 30 pack-years. Furthermore, women with a strong family history of breast, ovarian, colorectal, or endometrial cancer, as well as those diagnosed with triple-negative breast cancer before the age of 60, should be offered genetic counseling to evaluate hereditary cancer risks, such as mutations in BRCA1 or BRCA2 genes. This genetic assessment facilitates the development of personalized prevention and screening strategies. In addition to screening, lifestyle modifications—including smoking cessation, weight management, and engagement in regular physical activity—play a critical role in mitigating the risk of developing second primary cancers and associated comorbid conditions. It is essential that primary care providers maintain close collaboration with oncology specialists to deliver evidence-based care, facilitate appropriate referrals, and ensure comprehensive long-term follow-up for patients at elevated risk (Runowicz et al. 2016).

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SECOND PRIMARY CANCERS IN COLORECTAL CANCER SURVIVORS

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1. Epidemiology of colorectal cancer

Colorectal cancer (CRC), originating from uncontrolled cell proliferation in the colon or rectum, represents a formidable global health challenge. It stands as the third most diagnosed cancer across both genders and the second leading cause of cancer-related mortality worldwide (Abreu Lopez et al., 2024). GLOBOCAN 2020 data underscore this impact, reporting approximately 1.9 million new CRC cases and 935,000 associated deaths in 2020. These figures collectively account for an alarming 9.4% of all cancer-related deaths globally, signaling a critical area for focused medical and public health intervention (Morgan et al. 2023).

The distribution of CRC incidence and mortality varies significantly across regions, influenced by a complex interplay of behavioral, systemic, and socioeconomic factors. Diets high in processed foods, physical inactivity, and unequal access to preventive healthcare—including screening and timely follow-up—contribute to these disparities (Carethers and Doubeni 2020). High-income countries (HICs) report CRC incidence rates three to four times greater than low- and middle-income countries (LMICs). However, HICs generally exhibit lower mortality rates due to superior diagnostic tools, more effective treatments, and well-established screening programs.

Highest incidence rates are observed in Australia and New Zealand (35.3 per 100,000), Northern Europe (32.0), and Southern Europe (31.5) (Figure 1). Conversely, regions such as Western Africa, Middle Africa, and South-Central Asia report significantly lower incidence rates, typically ranging from 5.5 to 6.5 per 100,000 individuals (Figure 1). The declining CRC incidence in HICs since the late 1990s is largely attributed to lifestyle improvements, such as increased fiber intake and physical activity, alongside widespread colonoscopic screening and precancerous lesion removal. Many LMICs are experiencing a rise in CRC cases, likely driven by aging populations and the adoption of westernized lifestyles. Limited access to early detection tools in these regions often leads to later diagnoses and worse outcomes. Inadequate treatment infrastructure and cultural barriers further exacerbate the CRC burden in LMICs (Abreu Lopez et al. 2024).

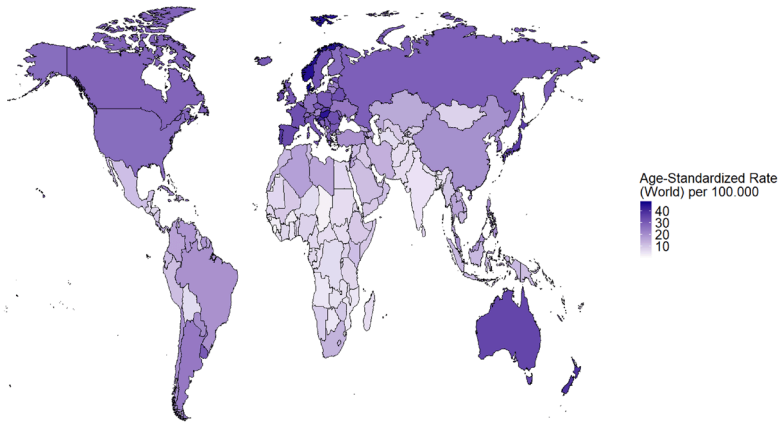


Figure 1: Global incidence of colorectal cancer in 2022, age-standardized rate per 100,000 individuals (Meklin, Syrjänen, and Eskelinen 2020).

The epidemiology of colorectal cancer (CRC) is profoundly shaped by the availability and effectiveness of screening programs. Therefore, screening is not merely a clinical tool but a crucial factor influencing global and regional CRC epidemiological trends (Shaukat et al. 2021; Abreu Lopez et al. 2024). Beyond geographical variations, a notable sex-based disparity in CRC epidemiology is evident, with males consistently exhibiting higher rates of both incidence and mortality compared to females. These disparities may stem from variations in screening participation, clinical presentation, tumor biology, and underlying molecular mechanisms.