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Decoding the mechanisms behind second primary cancers

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Abstract

Second Primary Cancers (SPCs) are defined as cancers that develop either simultaneously or metachronously in the same individual who has been diagnosed with and survived one primary cancer. SPCs exhibit a high incidence rate and represent the primary cause of mortality among survivors of first primary cancers. There is growing concern about the dangers of SPCs. This review summarizes recent studies on the mechanisms of SPCs, including the roles of genomic changes after first primary cancer (FPC) treatments, stromal cell phenotypic and metabolic changes, hormone levels and receptor expression, immunosuppression, aberrant gene methylation, EGFR signaling, and cell-free DNA in SPC development. This comprehensive analysis contributes to elucidating current research trends in SPC mechanisms and enhances our understanding of the underlying pathophysiology. Furthermore, potential applications of intratumoral microbes, single-cell multi-omics, and metabolomics in investigating SPC mechanisms are also discussed, providing new ideas for follow-up studies.

Keywords Second Primary Cancers, Mechanisms, Tumorigenesis, Immune

Introduction

Second Primary Cancers (SPCs) are defined as cancers that develop either simultaneously or metachronously in the same individual who has been diagnosed with and survived one primary cancer [1]. The significance of SPCs stems from their high incidence and substantial impact on first primary cancer (FPC) survivors. The incidence of SPCs varies widely, ranging from 2.4% to 19.0% [2–4]. A previous meta-analysis, encompassing a pooled cohort of 9,617,643 cancer patients, of whom 677,430 developed SPCs, examined the absolute numbers of patients with various types of FPCs who subsequently developed SPCs. The study revealed that among 1,825,198 breast cancer patients, 1,181,621 prostate cancer patients, and 711,504 skin cancer patients, 117,178, 111,150, and 76,517 respectively developed SPCs, ranking these three cancer types as the most prevalent in terms of SPC occurrence. Upon analyzing the incidence of SPCs among patients with various FPCs, the study revealed that patients with primary ureteral cancer exhibited the highest SPC incidence

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of 27.0%, followed by those with primary penis cancer (17.6%) and primary bladder cancer (15.8%) [5]. FPC survivors face an SPC risk 1.27 to 2.6 times higher than that of the general population [6, 7], with a 10–14% increased likelihood of developing SPCs [8, 9]. SPCs significantly impact FPC mortality, increasing the risk of death for FPC survivors by 33% in women and 45% in men.SPCs represent a leading cause of mortality among FPC survivors [10].

While SPC pose a significant threat to patients who have survived FPC, the precise mechanisms underlying SPC tumorigenesis remain a subject of debate. The molecular pathways involved in the development of general cancers encompass genetic mutations, aberrant signaling pathways, epigenetic alterations, tumor microenvironment as well as immune factors [11–18], all contributing synergistically to tumor initiation and progression.

While FPCs and SPCs share certain similarities in their pathogenesis, there are also notable differences between them. The key differences in their mechanisms can be summarized as follows:

Treatment-Related Factors: The emergence of SPCs may be intricately linked to the adverse effects of cancer therapies, particularly chemotherapy and radiotherapy. These treatments, while targeting and eliminating FPC, can inadvertently damage normal cells, thereby elevating the risk of SPC development. For instance, peroxides generated during FPC radiotherapy have been implicated in SPC induction [19]. Radiation-cell interactions lead to the production of free radicals that convert to peroxides, which then infiltrate unaffected cells [20, 21], inducing chromosomal damage and consequently radiation-induced bystander genetic damage, potentially contributing to SPCs.

Immune System Status: While the onset of FPCs may be associated with immune dysfunction, the development of SPCs can be further influenced by the immunomodulatory effects of cancer treatments. Immune cells and cytokines play pivotal roles in SPC development [20]. During FPC radiotherapy, lymphocytes and macrophages stimulated by radiation [22] amplify the production of inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, TNFα, TGFβ) in unaffected cells. These cytokines promote SPC development post-radiotherapy by stimulating cell growth/proliferation, inhibiting cancer cell apoptosis, recruiting type 1 macrophages to augment inflammatory responses, and modulating immune responses [23–28].

Further Implications of Genetic Factors: Beyond their role in FPC development, genetic factors may continue to influence the emergence of SPCs. Hereditary tumor susceptibility genes in patients with hereditary tumor syndromes have been implicated in the development of SPCs or multiple primary cancers[29]. For example, germline p53 mutations in Li-Fraumeni syndrome patients increase the risks for various cancers, including breast cancer, osteosarcoma, soft tissue sarcoma, brain tumors, adrenocortical carcinoma, and leukemia [30–34].

Although SPCs significantly impact FPC survivor survival and quality of life, the mechanisms underlying SPC occurrence remain controversial. Some studies suggest that immune cells and cytokines play key roles in SPC development, while others propose that hereditary tumor susceptibility genes underlie SPC formation. To date, no comprehensive review has systematically examined SPC mechanisms. Therefore, this review summarizes recent studies on SPC mechanisms and discusses the potential applications of intratumoral microbiology, single-cell multi-omics, and metabolomics in exploring SPC mechanisms, thereby providing insights for future research.

Risk factors of second primary carcinogenesis

Summarizing the risk factors associated with second primary cancers can help elucidate the potential relationships between multiple primary cancers and their common pathogenic factors. It is beneficial to further explore the molecular mechanism and biological pathway underlying second primary cancer development. We have identified and categorized the SPC risk factors including: tobacco and alcohol, obesity and diet, virus infection, genetic predisposition and pathways, and treatment-related factors.

Tobacco and alcohol

In a study of 25,000 subsequent cancers occurring in individuals with primary tumors at sites associated with tobacco and alcohol use (e.g., oral cavity, pharynx, esophagus, larynx, lung, and bronchus), more than 11,000 recurred at sites linked to tobacco and alcohol consumption. This finding underscores the enduring relationship between these substances and the development of second primary cancers [35].

Tobacco

Tobacco exposure induces the expression of urokinase-type plasminogen activator (uPA), leading to plasmin-dependent degradation of the extracellular matrix (ECM) and enhanced cell migration. This mechanism may contribute to the development of multiple primary tumors in patients with head and neck cancer [36]. Continued smoking following successful treatment of head and neck cancer significantly elevates the risk of developing second primary cancers (SPCs) [37–39]. This increased risk may be attributed to tobacco-induced activation of the epidermal growth factor receptor (EGFR) pathway [40]. EGFR stimulation activates ERK1/2, increasing uPA expression

[41, 42]. uPA cleaves plasminogen into ECM-degrading plasmin [43, 44], promoting tumor cell invasion and metastasis [36, 45, 46]. This mechanism may contribute to SPC development with a common clonal origin in smoking head and neck cancer patients [47–49]. Since uPA-uPAR binding stimulates EGFR and downstream ERK signaling [50] tobacco may activate an EGFR-ERK-uPA feedback loop, amplifying its carcinogenic effects.

Alcohol

The interaction between genetic factors, environmental alcohol consumption, and the ALDH2-2 allele increases the risk of multiple Lugol-voiding lesions (LVLs), which are characterized by dysplastic or hyperkeratinized unstained epithelium [51]. This interaction subsequently drives the development of second primary esophageal squamous cell carcinoma (ESCC) in patients with head and neck squamous cell carcinoma (HNSCC). The aldehyde dehydrogenase 2 (ALDH2) gene allele (ALDH2-2) is strongly associated with the occurrence of multiple LVLs [52, 53]. Chronic drinkers with the ALDH2-2 allele, who lack compensatory mechanisms for acetaldehyde elimination, exhibit elevated levels of LVLs [54]. As high acetaldehyde exposure from exhalation may contribute to the development of multiple LVLs [52].

HNSCC patients frequently develop second primary ESCCs [54–56], and multiple LVLs associate with high head and neck/esophageal multiple cancer risk [57, 58] and predict ESCC onset. Consequently, the presence of multiple LVLs may facilitate the development of secondary ESCCs in patients with HNSCC [52, 59–61]. In conclusion, alcohol consumption induces the formation of multiple LVLs in patients carrying the ALDH2-2 allele through complex genetic and environmental interactions. This process subsequently increases the susceptibility to second primary ESCCs in HNSCC patients [53].

Obesity and diet

Obesity is a well-established risk factor for multiple cancers, such as endometrial, colon, esophageal, kidney, pancreatic, and postmenopausal breast cancers, and is implicated in SPC development [62]. Moreover, factors including obesity, physical inactivity, and reproductive characteristics play a crucial role in the development of hormone-responsive tumors, particularly malignancies of the breast, uterus, ovaries, and prostate, as well as colorectal cancer [35]. Although the direct association between diet and SPCs remains incompletely elucidated, dietary factors, in conjunction with alcohol and tobacco consumption, exacerbate the risk of SPCs in patients with oral and pharyngeal cancers [63].

Virus infection

Viral infections, particularly Human papillomavirus (HPV), human immunodeficiency virus (HIV), human herpesvirus 8, Epstein-Barr virus (EBV), hepatitis B and C viruses, and Helicobacter pylori, play crucial roles in the development of SPCs [35, 64]. For instance, patients with one HPV-related cancer exhibit an elevated risk of developing another HPV-related SPC. Additionally, HPV infection is implicated in the concurrent occurrence of cervical and anogenital tract cancers, as well as oral cancers [62].

Genetic predisposition and pathways

Patients with hereditary cancer susceptibility syndromes carrying germline mutations exhibit an elevated risk of developing primary tumors at multiple sites, indicating a potential association between these germline mutations and SPC. For example, hereditary cancer predisposition syndromes, such as Lynch syndrome (formerly known as hereditary non-polyposis colorectal cancer or HNPCC), are associated with an elevated risk of SPCs in multiple organs, including the uterus, ovaries, bile ducts, small intestine, and renal pelvis. These syndromes are frequently associated with mutations in DNA mismatch repair genes, particularly MSH2 and MLH1 [65].

Furthermore, single nucleotide polymorphisms (SNPs) have also been implicated in an increased risk of developing SPC. Comparing individuals with multiple primary cancers versus cancer-free controls identified 22 potentially associated mutations. Of these, 10 mutations remained statistically significant when comparing patients with multiple cancers to those with a single cancer [66]. For instance, the rs7872034 (SMC2 missense variant) and rs143745791 (NCBP1 missense variant) showed stronger associations with the combination of primary breast cancer and any additional cancer compared to cancer-free individuals. These variants also demonstrated significant associations with the occurrence of breast cancer along with additional cancers, as opposed to breast cancer alone. The burden of oncogenic SNPs increased with co-morbid thyroid and breast cancers compared to just breast cancer [67]. Considering the apoptotic role of FAS/FASLG [68, 69] and the associations between their polymorphisms and cancer risk [70–73], Lei et al. [74] hypothesized that FAS/FASLG polymorphisms might influence the risk of developing SPCs. Indeed, head and neck squamous cell carcinoma (HNSCC) patients with FAS-670 AG/GG or FASLG-844 CT/TT variant genotypes had significantly higher SPC risk, increasing with more combined risk genotypes. Thus, FAS/FASLG polymorphisms could potentially serve as biomarkers for assessing SPC risk in HNSCC patients. Additionally, studies have demonstrated that

p21 polymorphisms in HNSCC patients are also associated with an increased risk of developing SPCs [75–77].

Moreover, specific signaling pathways have been implicated in the development of SPCs. For example, in patients with concurrent malignant melanoma and renal cell carcinoma, genetic variations in the PI3K/mTOR signaling pathway have been identified as a potentially significant common risk factor [78–80].

For easy reference, we've summarized key germline mutations, single nucleotide polymorphisms (SNPs), and signaling pathways related to SPCs in Tables 1, 2, 3.

Treatment

Treatment for FPC, particularly radiation therapy and certain hormone therapies, can also contribute to SPC development. For instance, radiation therapy for breast cancer increases the risk of lung, esophageal, and sarcoma development. Similarly, pelvic radiation therapy for cervical and uterine cancers has been associated with an elevated risk of acute leukemia [35]. In patients with retinoblastoma, mutations in the RB1 gene enhance radiosensitivity, thereby predisposing these individuals to radiation-induced malignancies such as osteosarcomas, soft-tissue sarcomas, and melanomas [81]. Additionally, Hodgkin's lymphoma survivors undergoing radiotherapy face a substantial risk of developing breast, lung, and other cancers [82]. Certain hormone therapies, such as

Table 2 Examples of single nucleotide polymorphisms (SNPs) that increase the risk of developingmultiple primary cancers

PMID/DOI	SNP/Gene	Major component cancers
36199081	rs7872034/SMC2 rs143745791/NCBP1	Breast cancer with other cancer
36199081	rs141647689	Bladder Cancer Prostate Cancer
	rs535484207 rs139586367 rs191064896	Lymphoid Neoplasms Prostate Cancer
	rs191064896	Lymphoid Neoplasms Breast Cancer
	rs555607708 (CHEK2) rs146381257 (ZNF106)	Prostate Cancer Breast Cancer Lung Cancer Bladder Cancer Lymphoid Neoplasms
	SLC6A2 ATM CHEK2 SAMHD1 BRCA2	Multiple primary cancer
	ATM	Prostate Cancer with other canc
	BRCA1 BRCA2	Breast Cancer with other cancer
20501759	FAS-670 AG/GG FASLG-844 CT/TT	Head and neck cancer with other cancer
19955391 34078296	P21 p27	Head and neck cancer with other cancer
24113849	TNF-α−238	Non-small cell lung cancer as SPC

Table 1 Examples of genetic mutations and hereditary cancer susceptibility syndromes that increase the risk of developing multiple primary cancers

PMID/DOI	Gene	Hereditary Cancer Susceptibility Syndromes	Major Component Cancers
24635432 14970275	MSH2 MLH1 MSH6	Lynch syndrome	Hereditary nonpolyposis colorectal cancer (HNPCC) Corpus uteri cancer Ovary cancer Stomach cancer Pancreas cancer Small intestine cancer Renal pelvis cancer
10.1023/B:JOMG.0000048770.90334.3b	BRCA1/2	Hereditary breast and ovarian cancer syndrome	Breast cancer Ovarian cancer
19204208 9554443	p53	Li-Fraumeni syndrome	Sarcoma Brain cancer Breast cancer Adrenocortical carcinoma
24778394	PTEN	Cowden syndrome	Breast cancer Thyroid cancer Endometrial cancer
15492928	CHEK2	/	Thyroid cancerProstate cancerBreast cancerKidney cancer
16391368 24635432	RB1	/	Retinoblastoma Osteosarcomas Soft- tissue sarcomas Melanoma

Table 3 Examples of pathways that increase the risk of developingmultiple primary cancers

PMID	Pathway	Cancers
36313724	EGFR	Co-occurrence of breast and lung cancers
34067022	PI3K/mTOR	Co-occurrence of melanoma and renal cellcarcinoma
22577058	PI3K/PTEN/AKT/MTOR	Second primary cancer after head and necksquamous cell carcinoma

tamoxifen used in breast cancer treatment, have been associated with an increased risk of endometrial cancer [35].

Mechanisms of second primary carcinogenesis

Genomic changes

DNA damage

Radiotherapy-induced DNA single-strand breaks (SSBs) can initiate senescence and serve as a mechanism for SPC initiation. Senescent cells may escape cell-cycle arrest, giving rise to mutant and invasive daughter cells with cancerous characteristics [83]. Standard radiotherapy protocols targeting FPCs [84] produce off-site doses resulting in SSB accumulation in normal fibroblasts at the planning target volume (PTV) edge [85]. Reduced poly(ADP-ribosyl)ation (PARylation) capacity impairs SSB repair [86, 87]. In fibroblasts, the accumulation of unrepaired SSBs does not cause death but upregulates senescence-associated p16, inducing early senescence [88–91].

Unlike persistent double-strand breaks (DSBs) causing permanent tumor-suppressor cell cycle arrest [92–97], radiotherapy-induced persistent SSBs allow mutation and senescence escape [90, 98]. Cells with persistent SSBs initially senesce but some re-enter the cell cycle, producing daughter cells with precancerous but not fully tumourigenic features [99, 100]. These daughter cells express precancerous transformation biomarkers, such as post-senescence neoplastic emergence (PSNE) genes and epithelial-mesenchymal transition (EMT) markers, and can form small carcinomas in mice, demonstrating oncogenic potential [99, 101–103].

Consequently, SSB-induced cellular senescence may play a role in initiating SPCs.

Telomere damage

Patients with shortened or damaged telomeres following chemotherapy or radiotherapy may be at an elevated risk of developing SPC [104]. First primary cancer (FPC) therapy results in significant telomere shortening, reduced telomerase activity, and decreased expression of human telomerase reverse transcriptase (hTERT) and telomere-binding proteins (TPP1, POT1)) [105]. Samples exposed to chemotherapy exhibit shortened telomeres and reduced telomerase activity compared to untreated samples [106].Patients undergoing chemotherapy demonstrate shorter telomeres compared to healthy controls [107]. Ionizing radiation has also been shown to impair telomere integrity in vivo [108, 109].

Telomere loss from radiotherapy causes chromosomal instability, mainly through the breakage-fusion-bridge (B/F/B) cycle (Fig. 1). Telomere-free fused sister chromatids form bridges during replication that break when pulled to daughter cells. One daughter then has an inverted duplication chromosome end lacking a telomere, while the other have a deletion at the end. Both replicate aberrantly, continuing the B/F/B cycle. Besides end amplifications, telomere loss can cause arm amplifications and transfer anomalies to other chromosomes, elevating instability [110–112].

Telomere damage-induced genomic instability may enable cancer evolution by accelerating genetic changes [113, 114].Firstly, B/F/B cycles create daughter cells with inverted repeat chromosome ends associated with gene amplification [115] and cancer [116–118].Second, short telomeres associate with increased head and neck, bladder, lung, and renal cancers [119]. Familial thyroid cancer patients show more telomere damage than spontaneous cases, potentially underlying cancer-enabling genomic instability [120, 121]. Thus, FPC therapy-induced

(See figure on next page.)

Fig. 1 Telomere loss-induced chromosome instability related to the breakage-fusion-bridge (B/F/B) cycle after radiotherapy and chemotherapy. First primary cancer radiotherapy and chemotherapy cause telomere breakage. Replicating telomere-free fused sister chromatids form bridges that break when pulled apart, causing one daughter cell to have an inverted duplication end lacking a telomere, while the other to have a deletion at the end. With continued telomere loss, B/F/B cycles accumulate inverted chromosome end repeats and progressive end deletions. Pink, green, and red arrows indicate subtelomeric sequence direction

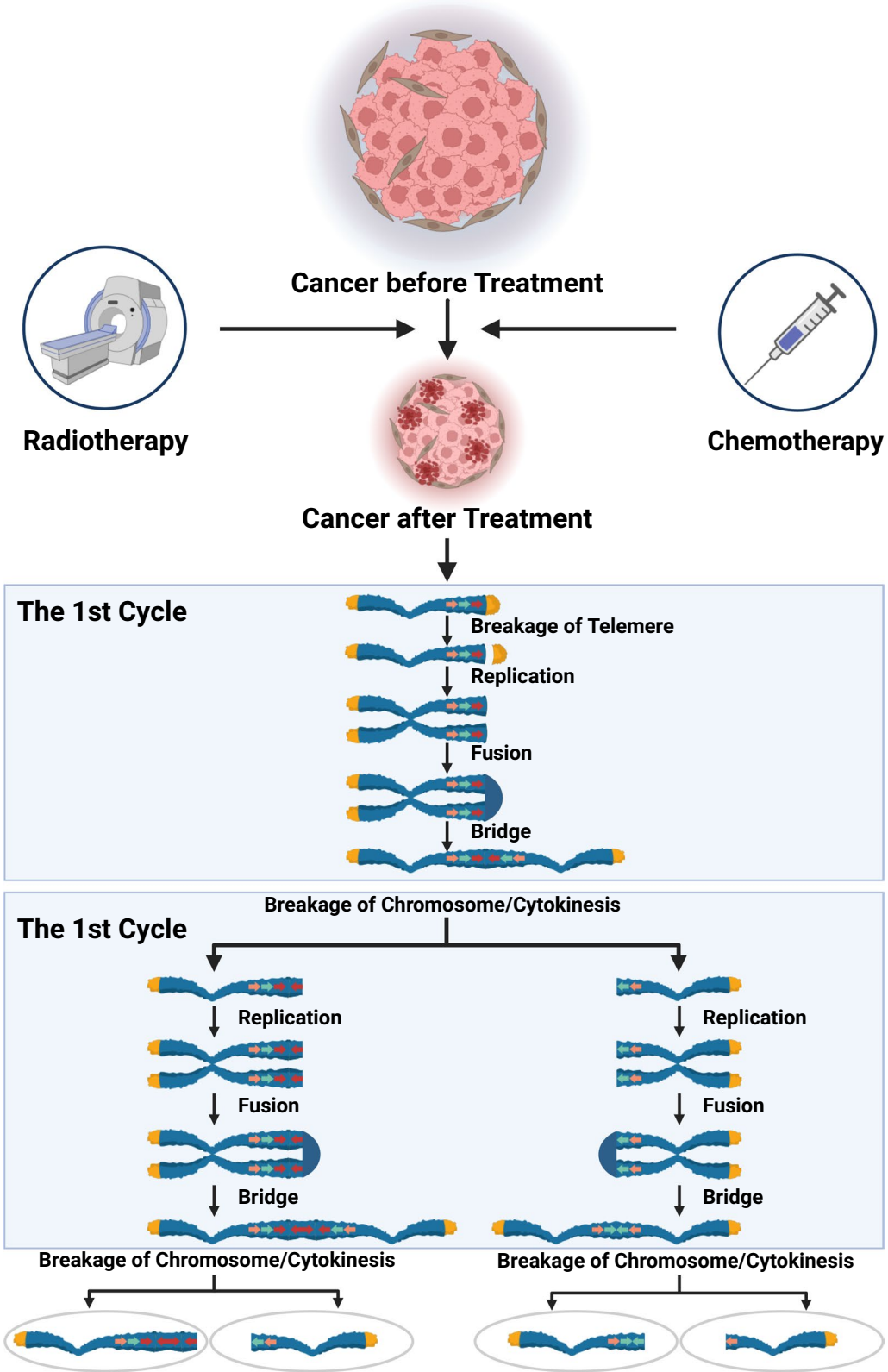

Fig. 1 (See legend on previous page.)

telomere damage may promote second carcinogenesis through genomic instability.

Phenotypic and metabolic changes in stromal cells

Phenotypic and metabolic alterations in stromal cells contribute significantly to the development of SPC [122] (Fig. 2). Chemotherapy induces oxidative stress in stromal cells adjacent to cancer cells, activating stress-related signaling pathways (e.g., HIF, NF-κB, SMAD, STAT3, JNK/AP1) [123]. This activation promotes various cellular processes, including glycolysis, mitochondrial dysfunction, autophagy, senescence, and the release of inflammatory cytokines. This stimulates cancer-associated fibroblast (CAF) differentiation, which facilitates tumor occurrence, progression, and metastasis [123–125]. Glycolytic/autophagic pathway upregulation in stromal fibroblasts increases energy-rich metabolite (e.g. lactate, ketones, glutamine) production, fueling

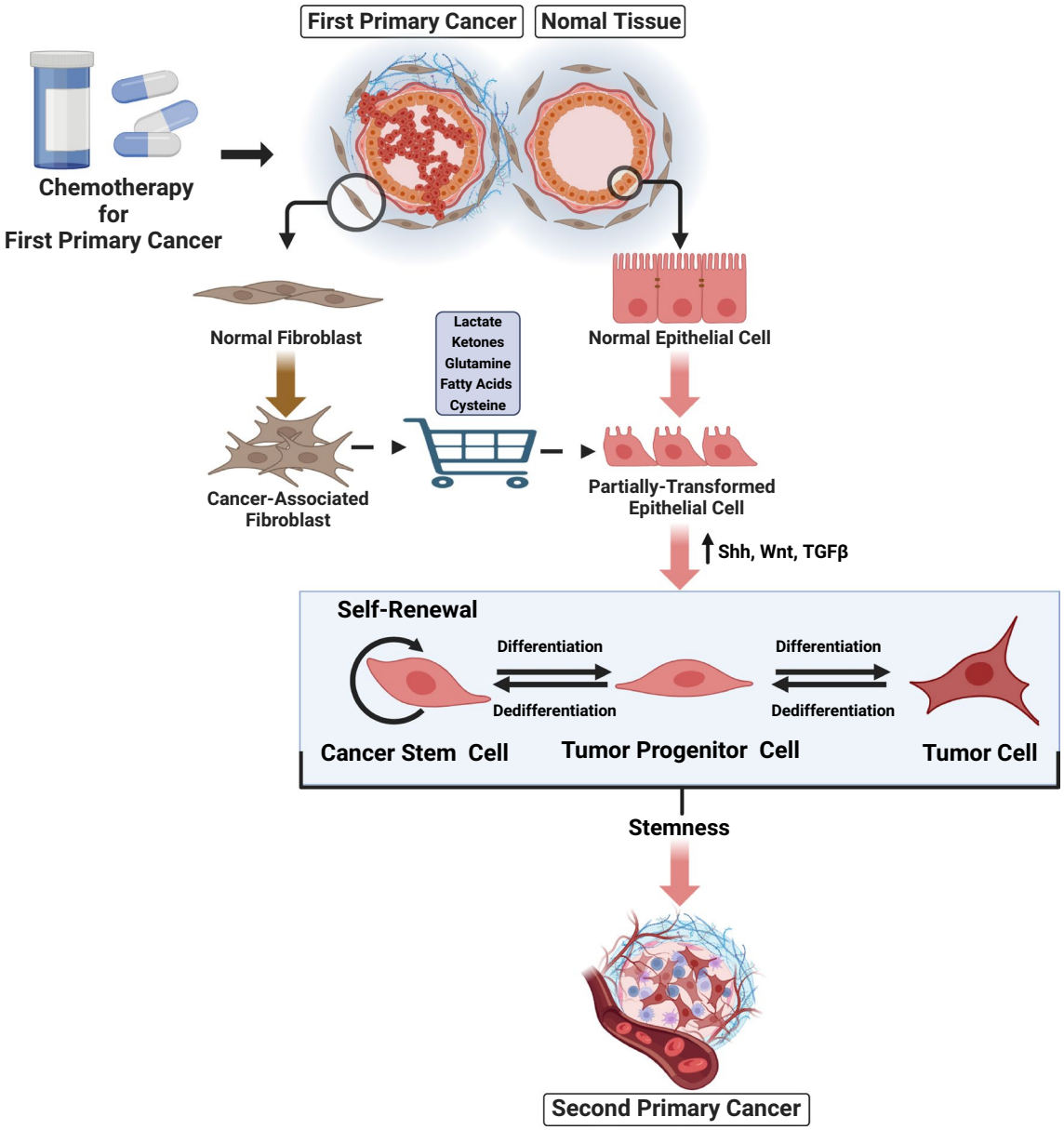

Fig. 2 Role of chemotherapy-induced cancer-associated fibroblast (CAF) in transforming partially transformed epithelial cells into second primary cancers (SPCs). In CAF-contacting partially transformed epithelial cells, pathways such as Shh, Wnt, and STAT3 involved in stem/progenitor cell renewal, metabolism, metastasis, and drug resistance may be activated. CAFs also produce metabolites like lactate, ketones, glutamine, fatty acids, and cysteine that fuel epithelial cell SPC transformation

cancer cell metabolic efficiency and promoting apoptosis resistance [126, 127]. Additionally, damaged fibroblasts promote the secretion of cytokines, such as IL-6, which aid in cancer cell survival and metastasis. Thus, metabolite-enriched microenvironments may enable malignant transformation of post-chemotherapy partially transformed epithelial cells, spurring new tumors [128, 129].

Chemotherapy also activates pathways related to stem/progenitor cell renewal, metabolism, metastasis, and chemoresistance (including Shh, Wnt, TGF-β, and STAT3) in breast cancer cells that are in contact with stromal cells [122]. Shh pathway activation associates with cancer development [130]. STAT3/Wnt pathways enhance oxidative phosphorylation, further promoting cancer cell growth [131, 132]. CAFs may stimulate stemness in impaired precancerous epithelial cells via Shh/Wnt/STAT3 pathway activation, triggering new oncogenic process [122].

Hormones

Serum insulin-like growth factor 1 (IGF-1)

Elevated serum IGF-1 levels are associated with an increased risk of second primary epithelial cancers (e.g., breast, lung, colon) in patients with head and neck cancer. Higher IGF-1 levels significantly increase SPC development risk [133]. In a breast cancer trial, lower IGF-1 levels were associated with fewer second primary cancers in premenopausal women [134]. The proposed mechanisms by which IGF-1 contributes to second primary cancer development include: (1) enhancing cell proliferation, apoptosis resistance, and clonal expansion of genetically damaged populations [135–138]; (2) regulating anti-apoptotic Bcl-xL/pro-apoptotic Bax ratios, affecting cell survival [139]; (3) increasing vascular endothelial growth factor (VEGF) (production as an angiogenesis regulator [140, 141]; (4) paracrine/endocrine promotion of second breast cancer growth by stromal cell-expressed IGF-1 [142]. Younger Hodgkin's lymphoma females have higher second breast cancer risk than older women [143, 144]. IGF-1 and growth hormone (GH) mediate pubertal mammary gland growth via estrogen [145–147]. Thus, Shanmugalingam et al. [142]hypothesized that elevated IGF-1/estrogen during puberty and stromal expressed IGF-1 may promote second breast cancer development, progression and metastasis by inhibiting apoptosis and inducing survival [148–150]. (5) Lung stromal cell expressed IGF-1 may act similarly through paracrine effects on bronchial epithelium in second lung cancers[142]. (6) Radiation-generated colon transformed cells may survive via increased IGF-1 bioactivity, enabling subsequent carcinogenesis through IGF-1R activation of proliferative, anti-apoptotic pathways, as in normal colon tissues, IGF-1 has a high affinity for IGF-1R and activates specific insulin receptor substrates [151].

Estrogen

High estrogen levels or estrogen receptor (ER) overexpression may contribute to concurrent thyroid and breast cancer [67]. Recent decades show increased breast cancer incidence associated with heightened exogenous/endogenous estrogens [152–154]. Estrogen binds ERα, regulating proliferation genes through genomic and non-genomic actions. ERα also enhances cancer cell survival/adaptation by responding to stresses and conditions [155]. Estrogen/receptor roles in thyroid cancer pathogenesis/progression include: ER overexpression in thyroid cancer [156, 157]; estrogen stimulation of benign/malignant thyroid cell growth in vitro [158–160]; estrogen-induced thyroid tumor cells' growth via mitogen-activated protein kinase (MAPK) activation [161, 162]; and involvement in the thyroid tumor microenvironment [163]. Thus, elevated estrogen/ER may underlie thyroid-breast cancer co-morbidity.

Indeed, estrogen/progesterone receptors were significantly higher in breast cancer specimens from women with co-occurring differentiated thyroid cancer versus controls with only breast cancer, regardless of cancer order [164–166]. ERa in the breast and thyroid can be activated by the MAPK pathway, promoting carcinogenesis [160, 167, 168]. Estrogen also binds GPR30 on the endoplasmic reticulum, activating MAPK pathway and thyroid/breast cancers [169, 170]. Overexpression of COMP may enable thyroid/breast cancer tumorigenesis/progression through estrogen signaling [171].

Immune suppression

Immunosuppression may increase second primary cancer risk. In addition to chemoradiotherapy effects, the association between secondary non-Hodgkin lymphoma (NHL) (a known immunosuppression-linked cancer [172, 173]) and melanoma/skin squamous cell carcinoma treated by surgery suggests immunosuppression promotes SPCs [174]. The first primary tumor may further impair immunity via chronic inflammation and defense mechanism suppression [175], enabling malignant cell immune evasion [176, 177]. Such immunosuppression may contribute to excessive SPC risk [178]. First primary cancer/treatment immunosuppression may also cause endogenous viral reactivation elsewhere, spurring second NHLs since Epstein-Barr virus (EBV) plays a key NHL infectious role [173] and post-transplant EBV reactivation drives post-transplant carcinogenesis [179]. Thus, immunosuppression may promote SPCs by facilitating the escape of malignant cells from immune surveillance and enabling viral reactivation.

Other mechanisms

Abnormal gene methylation

Abnormal gene methylation contributes to SPC development. For example, tissue inhibitor of metalloproteinase 3 (TIMP3) hypermethylation and transcriptional repression impedes its matrix metalloproteinase (MMP) inhibition. Since the extracellular matrix (ECM) enables malignant spread [180], this may promote invasion, tumorigenesis, metastasis and angiogenesis [181]. Thus, TIMP3 inhibition by hypermethylation/loss of MMP regulatory ability may promote SPCs [182].

Indeed, TIMP3 hypermethylation associated significantly with local recurrence-free survival in head and neck squamous cell carcinoma (HNSCC) [183]. Increased MMP9 expression in HNSCC histologically negative surgical margins also associated with SPC development [184], supporting hypermethylated TIMP3 enables SPC development through MMP disinhibition.

Hypermethylation of promoter regions often silences genes, causing loss of function. CCNA1 promoter hypermethylation inhibits apoptosis and cell cycle arrest by reducing CCNA1 expression. This promotes precancerous cell proliferative dominance and expansion of carcinoma-prone progenitor cells, enabling carcinogenesis [182].

EGFR signaling

Breast and lung cancers can co-occur as second primaries, and EGFR mutations may contribute to their concurrence [185]. Second primary lung cancers tend to follow first primary breast cancers [185, 186]. Zeng et al. observed a two-fold higher EGFR mutation rate in breast cancer patients with secondary lung cancer versus other cancer patients with secondary lung cancer, suggesting EGFR signaling may play a key role in concurrent breast-lung cancer[185]. Proposed EGFR signaling mechanisms in concurrent breast-lung cancer include:

(1) In solid tumors including breast cancer, EGFR pathway dysregulation via receptor/ligand overexpression, phosphatase deficiency, and altered dimerization causes carcinogenesis [187–189].
(2) EGFR can activate estrogen receptor (ER) signaling, which is important in primary lung cancer after breast cancer [185, 190, 191].
(3) EGFR is a growth factor receptor that activates intracellular cancer-associated signaling pathways [192, 193].
(4) EGFR overexpression associates with apoptosis and tumor angiogenesis [194, 195].

In summary, EGFR mutations may provide insights into the common cause of concurrent breast-lung cancers.

Circulating cell-free DNA

Chen et al.'s in vitro mouse tumor growth experiments after injecting normal cells transformed by free DNA suggest oncogenic circulating cell-free DNA (cf-DNA) may act like an intrinsic oncolytic virus [196]. Released by dividing cancer cells into body fluids, cf-DNA may transfect or transform adjacent/distant normal cells. Transformed cells may then proliferate into second primary cancers (Fig. 3).

Cf-DNA primarily leaks from apoptotic/necrotic cells into blood [197–199]. However, contrary to expectations of chemotherapy-induced apoptosis increasing cf-DNA, it significantly decreased cf-DNA [200]. Thus, Chen et al. speculated proliferating cancer cells may also release DNA during proliferation [196]. Thierry summarized three cf-DNA sources in cancer patients based on increased blood cf-DNA levels correlating with tumor cell numbers: healthy cells, malignant cells, tumor microenvironmental cells. Proliferation, apoptosis, necrosis, or secretion of cancer cell release cancer cell cf-DNA into circulation through structures like exosomes, microparticles, apoptotic bodies, nucleosomes, proteolipidonucleic acid complexes, DNA traps, or serum protein/cell membrane links [201].

Indeed, injected tumor DNA transformed mice [202], leading to the "genomic arrest" hypothesis where tumor-released cf-DNA transfects distant healthy cells, enabling metastasis [201, 203]. P. Anker et al. found after adding plasma from colorectal cancer mutant KRAS carriers (containing cf-DNA) to the culture medium, NIH/3T3 cells became carriers of both tumor and human KRAS mutations [204]. Patients who underwent resection of primary colorectal tumors with detectable tumor cf-DNA in plasma that can transform NIH-2T29 cells subsequently developed liver and lung cancers [205]. Thus, Chen hypothesized proliferating cancer cell-released cf-DNA may transfect or transform normal cells, explaining second primary cancer onset [196].

Prospects

The etiology and mechanisms of different second primary cancers require further investigation

Different FPCs may tend to develop different types of SPCs, and the mechanisms involved vary in different patterns. Further research is imperative to elucidate the etiology and mechanisms of different patterns.

Previous studies have analyzed the potential correlation between SPC occurrence and FPC, and explored the possible etiology and mechanisms of their patterns [5]. For instance, patients with first primary cancers occurring in four gynecological organs––namely the fallopian tube, uterus, vulva, vagina, and thyroid are more prone to develop second primary breast cancer and colorectal

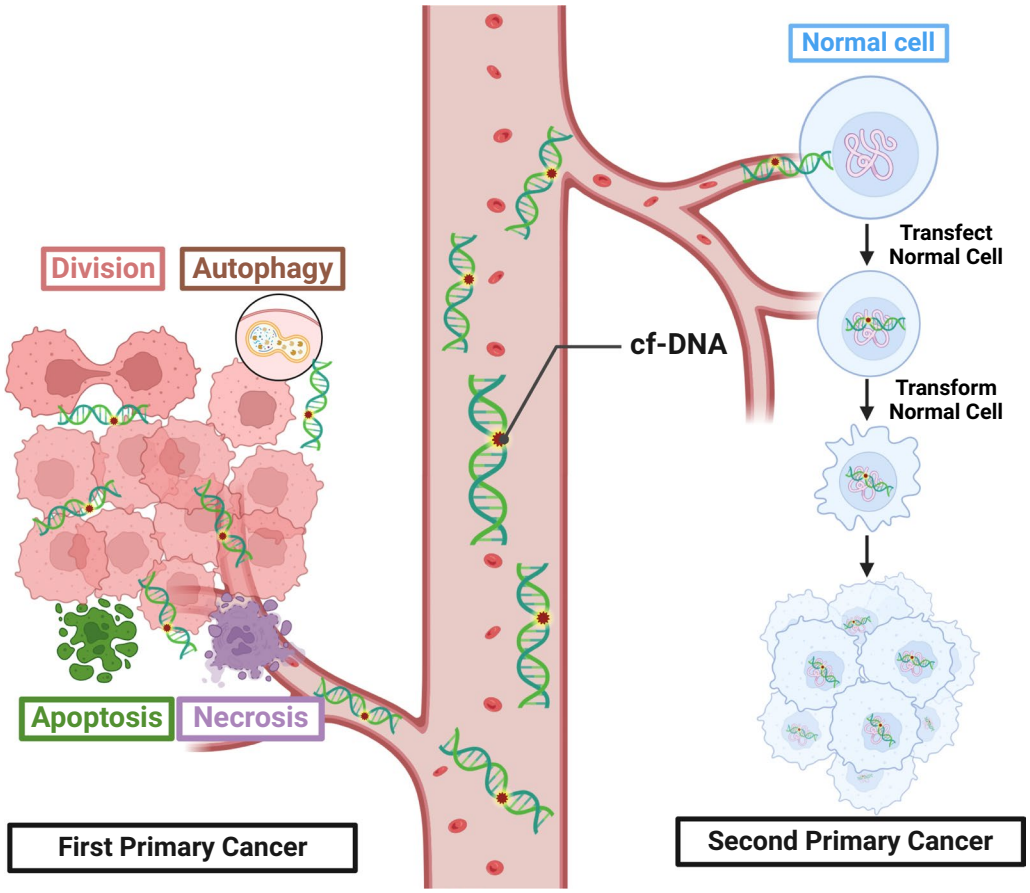

Fig. 3 First primary cancer (FPC) cell-free DNA induction of second primary cancers (SPCs) via normal cell transfection/transformation. FPC cells release circulating cell-free DNA via apoptosis, necrosis, autophagy, and division. This cell-free DNA transfects or transforms distant normal cells, inducing SPC formation

cancer. This phenomenon may be attributed to genetic susceptibility, the effect of hormone and radiation therapy after the FPC. Additionally, individuals with primary bladder or primary penile cancers have an increased likelihood of developing second primary prostate or lung cancer, which could be linked to their N-acetyltransferase genotype and smoking history. Furthermore, a high frequency of second primary bladder cancer is observed in patients with first primary ureteral cancer. This may be related to the clonal origin of upper urinary tract urothelial carcinoma, intraluminal seeding, and the treatment of ureteral cancer.

Additionally, a comprehensive monograph has analyzed the risk of subsequent cancers based on the primary site of cancer, providing insights into the potential etiology and risk factors involved [35].

Our study augments the existing knowledge on the etiology and mechanisms of various multiple primary cancers: ① During the subsequent development of second primary epithelial cancer in patients with head and neck cancer, elevated IGF-1 levels may contribute significantly. ② In the pattern of concurrent thyroid cancer and breast cancer, high levels of estrogen or overexpression of estrogen receptors (ER) may serve as contributing factors. ③ The development of second primary non-Hodgkin lymphoma (NHL) involves immunosuppression caused by the FPC. ④ In the pattern where breast cancer and lung cancer can mutually occur as each other's second primary cancer, EGFR mutations play a significant role.

Preventing SSB accumulation-induced senescence SPCs after FPC radiotherapy

SSB accumulation from off-target doses during FPC radiotherapy induces senescence and subsequent carcinogenesis, presenting a possible SPC mechanism and prevention opportunity. First, supplementing NAD + dietary precursors and modulating NAD + biosynthesis could prevent therapy edge senescence [206, 207], as

PARylation uses NAD + to repair SSBs and maintain DNA integrity [87, 208]. Second, senolytic drugs to clear senescent cells at radiotherapy end may prevent senescence-induced SPCs [209–211].

Further elucidating IGF-1's SPC role and predicting SPCs via IGF-1 levels

While studies show IGF-1 promotes proliferation, inhibits apoptosis, and stimulates angiogenesis in carcinogenesis [135–141], some highlight uncertainty around IGF-1's SPC role [133]. More observational research is needed to clarify IGF-1's contributions to specific SPCs and involved IGF-1R downstream pathways. Though IGF-1's SPC mechanisms remain unclear, elevated levels associate with SPC risk. Additional studies could thus assess serum IGF-1's SPC risk predictive utility, with clinical monitoring and early detection implications.

Investigating common risk factors in SPC development

High estrogen levels play carcinogenic roles in thyroid and breast cancers [152–154, 156, 157, 212, 213], presenting a potential common risk factor for both cancers. Although some studies speculate shared hormone receptors and pathways may enable thyroid-breast cancer co-occurrence [167], no evidence shows the first primary cancer alters estrogen to cause the second primary in the other organ. Similarly, while EGFR overexpression associates with breast and lung cancers [185], no evidence demonstrates directional carcinogenesis between lung and breast primaries via EGFR. Elucidating whether common risk factors play exact roles in cancer concurrences requires further SPC mechanism studies.

Intratumoral microbes in SPC

Cancer intratumoral microbiota may originate from mucosa, neighboring tissues, circulation, and the gut [214]. Intratumoral microbes promote carcinogenesis through DNA damage, mutation, oncogenic pathway activation, and tumor microenvironment influence [214]. Beyond its role in cancer development, microbiota also regulate therapeutic efficacy, providing potential microbiota modulation-based strategies [214]. However, the microbiota-SPC relationship remains unclear. Questions include: do SPC microbes originate similarly? Do microbes also drive SPCs through these mechanisms? Can SPC microbes be specifically regulated without disturbing other body microbiota in application to the treatment of SPC? Intratumoral microbes are highly heterogeneous in different tumor types and specific microbial metabolic pathways correlate with specific tumor types [215], so what role might Intratumoral microbial diversity play in the development of different SPCs?

Single-cell multi-omics for SPC mechanisms

Single-cell multi-omics analyses of genomes, transcriptomes, epigenomes and proteomes overcome batch limitations and enable detailed study of cancer cell/molecular biology. Single-cell cancer studies have resolved heterogeneity, microenvironment interactions, and evolutionary details [216], suggesting single-cell multi-omics applications in SPC. However, SPC mechanism data based on single-cell multi-omics is lacking; more single-cell omics SPC projects are needed. Key questions include: Do certain SPC mutations or pathway activations differ from corresponding primary cancers at the molecular level, identifiable via single-cell multi-omics? If so, personalized SPC treatments may be possible.

Metabolomics for SPC mechanisms and screening

A non-targeted metabolomics study identified higher 5-MTA, phenylacetylglutamine, and valylglycine levels in second versus first primary lung cancers [217]. Though associated with various primary cancer risks [218–221], links to SPC mechanisms need elucidation. However, metabolomics shows promise for SPC mechanism exploration and screening. Key questions: (1) Can metabolomics determine causal metabolite-SPC links? (2) The metabolic transformation observed in different tumor processes is heterogeneous [222], so whether the expression patterns of metabolites are different in different SPC? Can we predict SPC by monitoring the levels of certain metabolites in the blood? Do different SPCs show heterogeneous metabolic patterns enabling screening via blood metabolites? (3) Can blocking SPC-related metabolites in FPC patients prevent SPCs? (4) Are protective metabolite changes known? (5) Do immune cell metabolic aberrations also drive SPCs? (6) Do certain metabolites confer SPC treatment resistance and poorer outcomes?

Conclusion

Second primary cancers (SPCs) pose a serious global public health threat that endangers first primary cancer (FPC) survivors. While researchers have intensively studied SPC mechanisms in recent years, regarding exact causes many questions remain. This review synthesizes factors potentially influencing SPC development, including genomic changes, stromal cell phenotypic/metabolic changes, immunosuppression, hormonal changes, aberrant gene methylation, EGFR signaling, and circulating DNA. These factors may individually or jointly affect SPCs. However, their specific roles across various SPC types and potential interactions warrant further research. We also explored emerging fields like intratumoral microbiology, single-cell multi-omics, and metabolomics as promising approaches for elucidating SPC mechanisms.

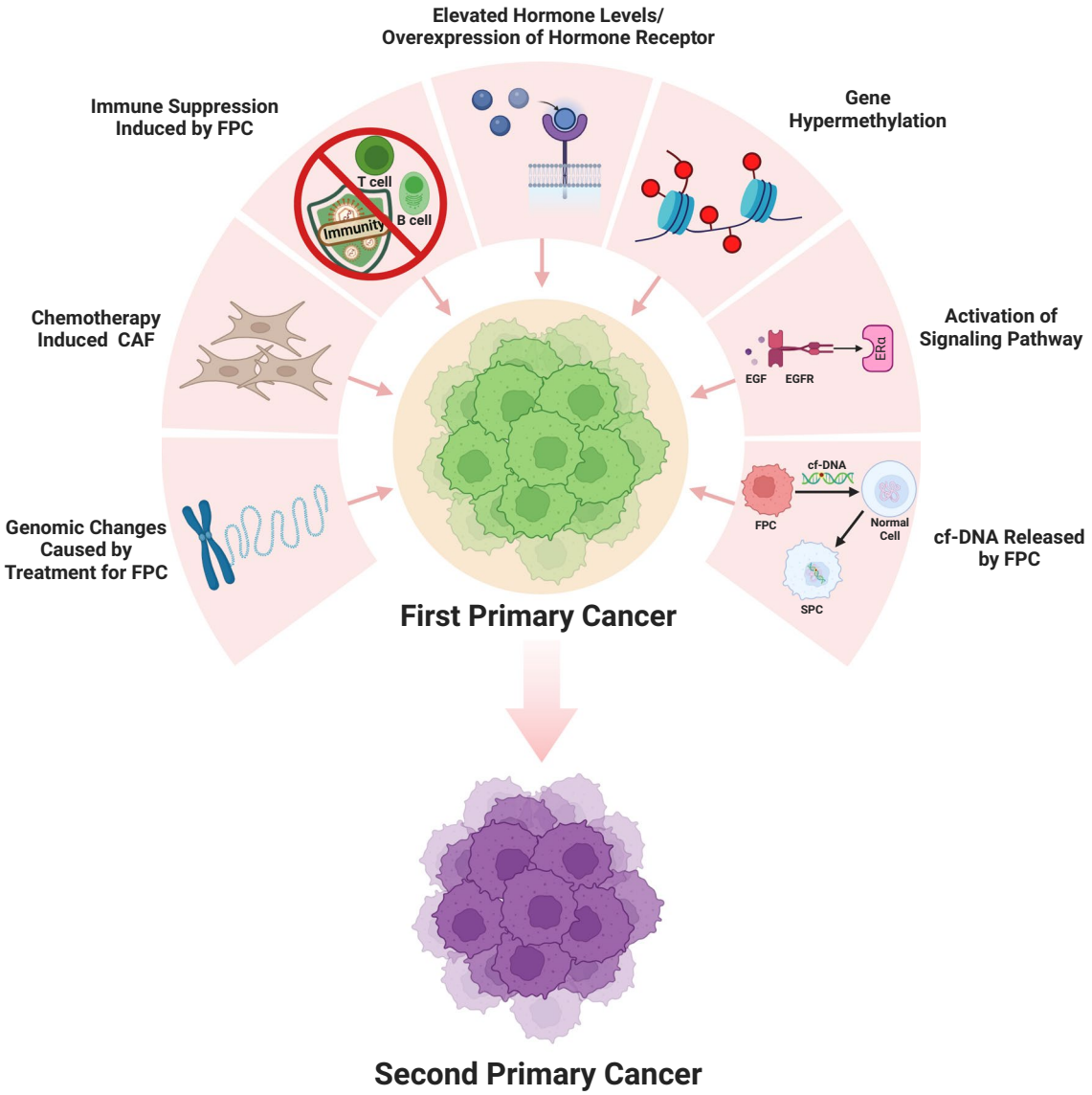

Fig. 4 Mechanisms of SPC occurrence and future research directions. SPC mechanisms include genomic changes caused by treatment for FPC, cancer-associated fibroblast (CAF) induced by chemotherapy, first primary cancer (FPC)-induced immunosuppression, abnormal gene methylation, signaling pathway activation, and FPC-released cell-free DNA

These cutting-edge technologies and approaches have the potential to provide deeper, more comprehensive SPC mechanism insights, thereby informing preventive and therapeutic advancements (Fig. 4).

Overall, SPC research still faces many challenges. Nevertheless,continued scientific and technological advancements, coupled with rigorous investigation, are expected to deepen our understanding of SPCs, potentially enabling more effective prevention strategies and treatment. Future research should aim to further elucidate specific factor roles in SPC development and their complex interrelationships. Simultaneously, more sensitive and specific methods for early SPC detection and innovative prevention strategies must be developed and validated. Through persistent and collaborative efforts, we can unravel the complex mechanisms underlying SPCs and translate these findings into life-saving outcomes for FPC survivors threatened by these devastating secondary malignancies.

Abbreviations

SPCs	Second primary cancers
FPC	First primary cancer
SSBs	Single-strand breaks
PTV	Planning target volume
PARylation	Poly(ADP-ribosyl)ation
DSBs	Double-strand breaks
PSNE	Post-senescence neoplastic emergence
EMT	Epithelial-mesenchymal transition
hTERT	Human telomerase reverse transcriptase
B/F/B	Breakage-fusion-bridge

SNPs	Single nucleotide polymorphisms
HNSCC	Head and neck squamous cell carcinoma
CAF	Cancer-associated fibroblast
IGF-1	Insulin-like growth factor 1
VEGF	Vascular endothelial growth factor
GH	Growth hormone
ER	Estrogen receptor
MAPK	Mitogen-activated protein kinase
NHL	Non-Hodgkin lymphoma
EBV	Epstein-Barr virus
uPA	Urokinase-type plasminogen activator
ECM	Extracellular matrix
SPC	Second primary cancer
LVL	Lugol-voiding lesion
ESCC	Esophageal squamous cell carcinoma
ALDH2	Aldehyde dehydrogenase 2
TIMP3	Tissue inhibitor of metalloproteinase 3
MMP	Matrix metalloproteinase
cf-DNA	Cell-free DNA

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Declarations

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