REVIEW

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The Tumor Suppressor *BRCA1/2,* Cancer Susceptibility and Genome Instability in Gynecological and Mammary Cancers

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Abstract

BRCA1 and *BRCA2* germline alterations highly predispose women to breast and ovarian cancers. They are mostly found within the TNBC (Triple-Negative Breast Cancer) and the HGSOC (High-Grade Serous Ovarian Carcinoma) subsets, known by an aggressive phenotype, the lack of therapeutic targets and poor prognosis. Importantly, there is an increased risk for cervical cancer in *BRCA1* and *BRCA2* mutation carriers that raises questions about the link between the HPV-driven genome instability and *BRCA1* and *BRCA2* germline mutations. Clinical, preclinical, and in vitro studies explained the increased risk for breast and ovarian cancers by genome instability resulting from the lack or loss of many functions related to *BRCA1* or *BRCA2* proteins such as DNA damage repair, stalled forks and R-loops resolution, transcription regulation, cell cycle control, and oxidative stress. In this review, we decipher the relationship between *BRCA1/2* alterations and genomic instability leading to gynecomammary cancers through results from patients, mice, and cell lines. Understanding the early events of *BRCA1/2*-driven genomic instability in gynecomammary cancers would help to find new biomarkers for early diagnosis, improve the sensitivity of emerging therapies such as PARP inhibitors, and reveal new potential therapeutic targets.

Keywords: *BRCA1- BRCA2-* gynecomammary cancers- breast cancer- ovarian cancer- cervical cancer- genome instability

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Introduction

Breast, cervical, and ovarian cancers are among the most threatening diseases for women's health around the globe (Ferlay et al., 2021). The combined incidences of those gynecomammary cancers in 2020 reached 3.18 million new cases, constituting thus more than the third (34.45 %) of all diagnosed cancer cases in females in the same year (Sung et al., 2021). Indeed, even considering both sexes, breast cancer had the highest incidence rate, with 2.26 million new cases, followed by lung cancer, with 2.21 million new cases in 2020 (Sung et al., 2021). Cervical cancer came fourth (601 127 new cases), and ovarian cancer came sixth (313 959 new cases) in incidence among women in 2020. Moreover, breast, cervical, and ovarian cancers registered 1.24 million of 4.43 million deaths by cancer in women in 2020 (Sung et al., 2021). Breast cancer was the first leading cause of death by cancer in 110 countries from 185, while cervical cancer ranked as the first deathful cancer in 36 countries, mostly in sub-Saharan Africa, South-Eastern Asia, Melanesia, and South America (Sung et al., 2021). Cervical cancer occurs mainly in low-income and middle-income countries (Islam et al., 2018; Ferlay et al., 2021), while in high-income countries, it is less frequent due to improved screening and vaccination programs (Cohen et al., 2019).

Breast, ovarian, and cervical cancers constitute a distinct group of cancers because of their shared risk factors, such as feminine sex, genetics (Ring et al., 2017; Yoshida, 2021), and genome instability markers (Miyai et al., 2004; Maxwell et al., 2017). Hereditary breast and ovarian cancers constitute 10 to 15% of all breast and ovarian cancer cases (Pal et., 2005; Yoshida, 2021) and most of them are related to *BRCA1* and *BRCA2* mutations (Yoshida, 2021; Quesada et al., 2022). In sporadic breast and ovarian cancer cases, somatic mutations of *BRCA1/2* genes are less common (6.6%) (Kwong et al., 2020), *BRCA1* DNA methylation was reported in sporadic breast and ovarian cancers, respectively in 32.6% and 15% of cases (Ruscito et al., 2014; Cai et al., 2016), while there is no evidence of *BRCA2* DNA methylation in these

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cancers (Collins et al., 1997). The contribution of *BRCA1* and *BRCA2* as cancer susceptibility genes in cervical cancer remains controversial (Johannsson et al., 1999; Thompson and Easton, 2002). HPV infection (95% of cases) is the primary factor of cervical cancer development (Waggoner and Chernicky, 2004). Of note, women with HPV-associated cervical cancer are at risk of developing HPV-associated breast cancer (Lawson et al., 2016).

Since their first discovery, *BRCA1* (Chr17q) and *BRCA2* (Chr13q) genes have constituted the major known contributors to human cancer genetic susceptibility (Miki et al., 1994; Wooster et al., 1995), especially in breast and ovarian cancers (Perez-Losada et al., 2011). Germline mutations in the *BRCA1* and *BRCA2* genes have also been implicated in increasing the susceptibility to prostate cancer among men (Umarane et al., 2023). Their function in DNA damage repair by homologous recombination (HR) is widely established (Roy et al., 2012; Isono et al., 2017). Indeed, *BRCA1* multifunctional domains interact with several actors such as 53BP1, BARD1, MRN complex, PALB2, and RAD51 to facilitate the choice, initiation, and execution of HR repair machinery to resolve double-strand breaks (DSBs), which are the most dangerous DNA damages of genome integrity (Roy et al., 2012; Isono et al., 2017). Besides, *BRCA2* is indispensable for recruiting the recombinase RAD51 to DSBs foci, which constitutes the ultimate step of the HR pathway (Roy et al., 2012). Nevertheless, they play other essential functions in maintaining genome integrity, such as chromatin remodeling, R-loops resolution, and stalled forks repair (Pathania et al., 2014; Tan et al., 2017; Zhang et al., 2017; Zhang et al., 2019). Moreover, *BRCA1/2* genes play other functions in cell cycle control, transcription regulation, and oxidative stress (Rodriguez et al., 2007; Norquist et al., 2010; Chiang et al., 2019; Renaudin et al., 2021).

About 4000 and 4675 pathogenic and likely pathogenic mutations were reported in *BRCA1* and *BRCA2* genes, respectively (Clinvar-*BRCA1* gene, 2023). Deletions are the primary genetic alterations affecting both genes, followed by insertions, point mutations, duplication, and indels (Clinvar-*BRCA1* gene, 2023). The origins of genetic alterations in the *BRCA1/2* genes are widely unknown. However, the large genomic rearrangements (LGRs) of the BRCA1 gene represent 10% of all the predisposing pathogenic variants, and they are caused mainly by the high density of Alu elements (41, 5%) in the BRCA1 gene (Smith et al., 1996). Of note, Alu elements are transposable elements causing several genomic alterations and are believed to be the source of human genetic diversity (Ade et al., 2013). Also, a *BRCA1* pseudogene near 5′ of the *BRCA1* gene constitutes a recombination hot spot that can cause several LGRs (Puget et al., 2002). The frequency of a pathogenic mutation depends on the ethnic origins of each population; for example, 185delAG is a founder mutation in the Ashkenazi Jewish population, causing both breast and ovarian cancers (Struewing et al., 1995). The current review will discuss the available literature on *BRCA1*/*2*-driven genomic instability and cancer susceptibility in breast, ovarian, and cervical cancers.

The Tumor Suppressor BRCA1/2, Cancer Susceptibility, and Genome Instability in Breast Cancer

Background

Tumor suppressors *BRCA1* and *BRCA2* are highly penetrant genes predisposing to breast cancer (Venkitaraman, 2019). The cumulative risk of breast cancer to the age of 80 was estimated to be 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers (Kuchenbaecker et al., 2017). Moreover, contralateral breast cancer is widespread among *BRCA1* (40%) and *BRCA2* (26%) carriers after 20 years of the primary diagnosis of breast cancer (Kuchenbaecker et al., 2017). Hence, heterozygous *BRCA1* and *BRCA2* germline mutations render mammary epithelial tissue an active "field" for tumorigenic development (Venkitaraman, 2014). Human hereditary biallelic mutations of *BRCA1* and *BRCA2* are not viable, except in some rare cases when biallelic *BRCA1* or *BRCA2* carriers live with Fanconi anemia disorder manifestations associated with recurrent early onset breast and ovarian cancers (Sawyer et al., 2015; Fang et al., 2020).

BRCA1/2-associated breast tumors are frequent (~70%) in triple-negative basal-like molecular subtype (Felicio et al., 2017), known for their poor prognosis due to the lack of therapeutic targets (Ge et al., 2022). Interestingly, *BRCA1*/*2*-associated breast tumors show higher sensitivity toward PARP inhibitors and platinum-derived therapy (Lord and Ashworth, 2016). Understanding the early genome instability of *BRCA1*/*2*-associated breast tumorigenesis would improve the progress and efficiency of these therapies and reveal other potential early actors (Fu et al., 2022). In this regard, clinical, preclinical, and in vitro studies provide enormous outcomes on the link between *BRCA1*/*2*-associated genome instability and breast tumorigenesis (Figure 1) (Xiao et al., 2014; Vohhodina et al., 2021; Wu et al., 2022). Indeed, emerging results contradict the old paradigm of the "two-hit" theory inducing *BRCA1*/*2*-associated breast tumors (Sedic et al., 2015; Vohhodina et al., 2021; Sun et al., 2022), and *BRCA1* or *BRCA2* haploinsufficiency remains the plausible alternative process of tumorigenesis through the induction of an early genome instability in human mammary epithelial cells (Figure 1A) (Bhatia et al., 2014; Pathania et al., 2014; Sedic et al., 2015; Vohhodina et al., 2021; Sun et al., 2022).

Results from patients

In malignant breast tumors harboring *BRCA1* or *BRCA2* mutation, the remaining wild-type allele was found inactivated by loss of heterozygosity (LOH), respectively, in 90% and 54% of *BRCA1* and *BRCA2* -associated breast tumors (Maxwell et al., 2017). This widely observed biallelic inactivation may represent an analogy to the "two-hit" theory of accelerated tumorigenesis in familial breast tumors (Konishi et al., 2011). However, due to *BRCA1* and *BRCA2* vital tumor suppressive functions, their complete inactivation in mammary epithelial cells can cause DNA damage, leading to cell cycle arrest and apoptosis (Figure 1A) (Konishi et al., 2011; Venkitaraman, 2014; Sedic et al., 2015). For this reason, the loss of heterozygosity must be preceded by

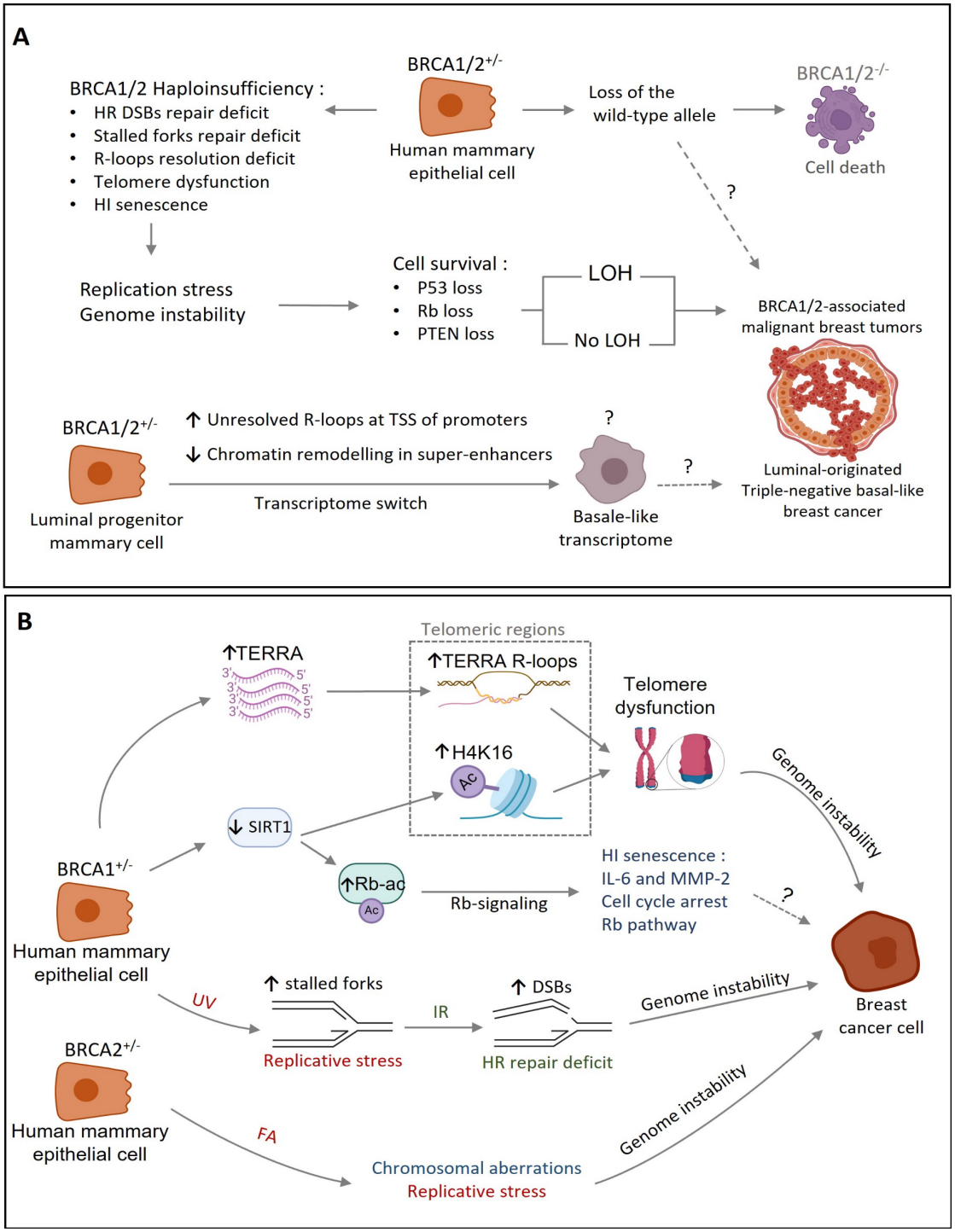

Figure 1. The Tumor Suppressor *BRCA1/2,* Cancer Susceptibility, and Genome Instability in Breast Cancer. **A** *BRCA1/2* heterozygous (*BRCA1/2*+/-) Human mammary epithelial cells (HMECs) present a *BRCA1/2* haploinsufficiency that leads to several molecular defects, including HR (homologous recombination) DSBs (double-strand breaks) repair deficit, the accumulation of unresolved stalled forks and R-loops, telomere dysfunction, and haploinsufficiency-induced senescence (HI senescence). The resulting genome instability may alter several genes involved in cell survival, such as P53, Rb protein, and PTEN. *BRCA1/2* loss of heterozygosity (LOH) may not be an early event of *BRCA1/2*-associated genome instability but rather a consequence of this later. BRCA1/2-associated breast tumors plausibly originated from *BRCA1/2* heterozygous (*BRCA1/2*+/-) luminal progenitor cells due to the role of *BRCA1/2* genes in resolving R-loops at promoters or super-enhancers of key genes of luminal differentiation, but also to the role of *BRCA1* in chromatin remodeling. **B** *BRCA1* haploinsufficiency (*BRCA1*+/- HMECs) causes TERRA-loops accumulation in telomeric and subtelomeric regions, leading to telomeric abnormalities and genome instability. *BRCA1*+/- HMECs in cell culture develop a telomeric dysfunction at early passages, then at late passages, they develop a type of senescence mediated by Rb signaling, qualified by haploinsufficiency-induced senescence (HI senescence). These consequences are correlated to a decreased expression of SIRT1 and increased acetylation of Rb protein and telomeric histones. The exposure of *BRCA1*+/- HMECs to UV (Ultras-violet) radiation induces replicative stress due to the accumulation of unresolved stalled forks, which collapse after exposure to IR (ionizing radiation), leading to DSBs accumulation and genome instability. BRCA2+/- HMECs exposed to formaldehyde (FA) show increased replication stress due to accumulated unscheduled R-loops, which may cause genome instability.

somatic alterations sustaining cell viability, such as those of the P53 or Rb genes (Sedic et al., 2015). Indeed, P53 and Rb losses occur frequently (relatively independently) in *BRCA1*-associated breast tumors (Patel et al., 2020); and P53 and PTEN losses (mutations) were estimated to precede *BRCA1* loss of heterozygosity in more than 80% of studied cases (Figure 1A) (Martins et al., 2012).

BRCA1 heterozygous (*BRCA1*+/-) mammary epithelial cells express limited amounts of functional *BRCA1* protein (Pathania et al., 2014) that does not suffice (haplotype insufficiency) to correctly perform several vital *BRCA1*-related functions, including homologous-recombination (HR) double-strand breaks (DSB) repair, stalled fork resolution, R-loop resolution, and chromatin remodeling (Figure1B) (Konishi et al., 2011; Pathania et al., 2014; Sedic et al., 2015; Zhang et al., 2017; Vohhodina et al., 2021; Sun et al., 2022). In *BRCA1* carriers, a monoallelic mutation may suffice to trigger genome instability in normal mammary epithelial cells, leading them to transformation (Sedic et al., 2015). Indeed, blood genomes analysis in family members carrying a founder *BRCA1* mutation revealed 23 deleterious mutations affecting genes implicated in tumorigenesis (e.g., BPTF and FOXP1), which are not present in non-carrier members (Xiao et al., 2014). Besides, a comparison between mother and daughter carriers revealed that daughter carriers develop de novo 9 deleterious mutations in addition to 14 deleterious mutations inherited from their mother carriers. Noteworthy, two of those deleterious mutations were found within repetitive sequences, and five were found within fragile sites, known as the most vulnerable sequences of the genome to DNA damage (Xiao et al., 2014). Another study by Litton and colleagues (2012) showed that *BRCA1/2* daughter carriers develop breast cancer earlier than their mother carriers, at 42 and 48 medians of age, respectively (Litton et al., 2012). This latter result may be explained by the accumulation of deleterious mutations in the genomes of daughter carriers (second generation), which carry more deleterious mutations (*BRCA1/2*-induced genome instability) than their mother carriers from the first generation (Xiao et al., 2014). In this model, *BRCA1/2* monoallelic mutation may promote genome instability all along the life of a *BRCA1/2* female carrier by generating potential deleterious mutations and genome instability, which increases the risk of developing malignant breast tumors.

Results from animal models

Mice heterozygous for the *BRCA1* gene do not develop spontaneous breast tumors as predisposed humans do, hypothetically due to some differences between species, such as the short lifespan in mice (Drost and Jonkers, 2009). However, biallelic inactivation of *BRCA1* or *BRCA2* genes in mice causes early embryonic lethality (Ludwig et al., 1997). Still, an additional mutation of the P53 locus can rescue embryos with *BRCA1* biallelic inactivation until adulthood (Xu et al., 2001). *BRCA1* conditional knockout in female mice (conditional in mammary tissue) carrying a P53 heterozygous mutation induced mammary tumors with the loss of the remaining wild-type P53 allele due to genome instability and the presence of similar genomic and histopathologic features to the human basal-like malignant breast tumors carrying both *BRCA1* and P53 mutations (Liu et al., 2007). However, in *BRCA1* heterozygous mice, P53 alteration did not significantly influence the levels of genome instability generated in normal breast tissues (Wu et al., 2022). Consequently, the role of P53 alterations in mammary transformation may be restricted to sustaining cell viability to overcome apoptosis after genome instability induction, at least in the mice model (Figure 1A) (Wu et al., 2022).

Reporter mice showed that homologous recombination (HR) is the primary double strand breaks repair mechanism in proliferating mammary tissue (pubertal and pregnant) compared to other tissue types (Kass et al., 2016). This reliance on HR in repairing DNA damage in proliferating mammary tissue may explain the higher risk of breast cancer conferred by *BRCA2* (or *BRCA1*) mutations in predisposed women (Kuchenbaecker et al., 2017). In humans, both *BRCA1* and *BRCA2* contribute to the resolution of R-loops, which, if accumulated, cause replicative stress and genome instability (Tan et al., 2017; Zhang et al., 2017). In mice, mammary tissue carrying *BRCA1* conditional knockout showed increased levels of R-loops in luminal cells and increased frequency of spontaneous tumors (Zhang et al., 2017). In addition, pregnant *BRCA2* homozygous mice showed reduced HR repair use in luminal and basal cells but decreased more in the luminal population (Kass et al., 2016). This specificity toward the luminal lineage of mammary tissue goes with several results generated at the human level (cell lines) in considering luminal progenitor cells as the origin of *BRCA1/2*-associated breast tumors (Figure 1A) (Sedic et al., 2015; Zhang et al., 2017).

Given that *BRCA1/2* heterozygous mutations do not cause spontaneous breast tumors in mice, the use of mice with this genetic background is valuable in studying the role of *BRCA1/2* heterozygosity in genome instability induction (Drost and Jonkers, 2009; Wu et al., 2022). Indeed, mice carrying a heterozygous *BRCA1* mutation developed early genomic instability by manifesting several genomic alterations (structural variations, copy number variations, and indels) in normal tissues from an early embryonic age (Wu et al., 2022). The breakpoints of structural variations (SVs) were enriched in repetitive sequences (54% of SVs) and multiple fragile sites of *BRCA1* heterozygous mice genomes (Wu et al., 2022). The analysis of those breakpoints revealed the use of error-prone non-homologous pathways to repair DSBs, including non-homologous end joining (492 repaired DSBs), microhomology-mediated end joining (75 repaired DSBs), and single-strand annealing with 2 repaired DSBs (Wu et al., 2022).

Results from cell lines

BRCA1 and *BRCA2* heterozygous human mammary epithelial cells express lower levels of *BRCA1* and *BRCA2* proteins, respectively (Pathania et al., 2014, Tan et al., 2017). A decreased pool of *BRCA1* or *BRCA2* proteins causes haploinsufficiency toward several *BRCA1/2* related functions, leading to genome instability in normal mammary epithelial cells of BRCA1/2 carriers (Figure

1A) (Sedic and Kuperwasser, 2016).

Exposure of immortalized (hTERT) BRCA1+/- HMECs (Human mammary epithelial cells) to UV-radiation induced the accumulation of unresolved stalled forks with no impact on homologous recombination double-strand breaks (HR DSBs) repair and other *BRCA1*-related functions (Pathania et al., 2014). When exposed to ionizing radiation, those resulting cells (pre-exposed to UV) showed decreased ability to recruit RAD51 to DSBs foci, which indicated an HR DSBs repair deficit (Figure 1B) (Pathania et al., 2014). The pool of *BRCA1* in heterozygous UV-pretreated HMECs was not sufficient to repair IR exposure consequences (DSBs), leading to DSBs accumulation and genome instability (Figure1B) (Pathania et al., 2014). These results show the limits of a decreased *BRCA1* protein intracellular pool within BRCA+/- HMECs in performing all the required functions, especially under stressful conditions (Pathania et al., 2014). Besides, the exposure of immortalized (HPV16 E6 and E7 oncogenes) *BRCA2*+/- HMECs to formaldehyde caused a decrease in the intracellular *BRCA2* protein pool, chromosomal abnormalities, and replication stress, as compared to their wild-type cells (Figure 1B) (Tan et al., 2017).

In immortalized (hTERT) *BRCA1*+/- HMECs, *BRCA1* haploinsufficiency causes a specific type of senescence, qualified by Haploinsufficiency-induced-senescence (HIS), which is mediated by Rb pathway activation (Sedic et al., 2015). Indeed, at early passages in cell culture, *BRCA1*+/- HMECs showed DNA damage response activation and multiple chromosomal abnormalities, including telomeric abnormalities. More importantly, luminal epithelial cells from breast lobules of *BRCA1* mutation carriers showed shorter telomeres than those from non-carriers. Mechanistically, this study showed that the SIRT1 intracellular pool decreased in *BRCA1*+/- HMECs, which triggers both haploinsufficiency-induced senescence and telomer dysfunction through activating acetylation of Rb protein and acetylation of telomeric histones leading them to destabilization (Figure 1B) (Sedic et al., 2015). Additionally, *BRCA1* participates in telomeric stability by regulating the long non-coding RNA TERRA (Telomeric Repeat RNA) expression and resolving TERRA-associated R-loops in telomeric and sub-telomeric regions. The accumulation of TERRA RNA and the unresolved TERRA-associated R-loops in *BRCA1*+/- HMECs (CRISPR-modified) causes telomeric abnormalities leading to genome instability (Figure 1B) (Vohhodina et al., 2021).

Most *BRCA1*-mutated malignant breast tumors are from the triple-negative basal-like subtype, known by basal mammary cell biomarkers and the negativity of estrogen and progesterone receptors (Popova et al., 2012). Besides, luminal progenitor cells are believed to be the origin of *BRCA1*-associated breast tumors (Sedic et al., 2015; Zhang et al., 2017). A transition from the luminal phenotype to the basal-like transcriptome may be the key to explaining the specific risk of breast cancer conferred by *BRCA1* haploinsufficiency (Zhang et al., 2019). Indeed, luminal mammary cells harbor increased transcriptional activity and active enhancers compared to basal mammary cells and consequently develop increased levels of DNA-RNA transcriptional secondary structures, R-loops (Gascard et al., 2015; Zhang et al., 2017; Zhang et al., 2019). R-loops promote the instability of common fragile sites due to collisions between transcription and replication (Helmrich et al., 2011). R-loops levels increased in *BRCA1*+/- luminal mature and progenitor cells compared to *BRCA1*+/- basal and stromal cells, indicating a luminal-specific *BRCA1* haploinsufficiency toward R-loops resolution (Zhang et al., 2017).

Immortalized (hTERT) *BRCA1*+/- HMECs and *BRCA1*+/- MCF10A (Immortalized non-tumorigenic HMEC line) cells show a reduced number of active super-enhancers (super-enhancer = cluster of enhancers) compared to their wild-type, *BRCA1*+/+ (Zhang et al., 2019). In both cell types (*BRCA1*+/- HMECs and *BRCA1*+/- MCF10A), the attenuation of some super-enhancers was observed and correlated with decreased expression of their downstream target genes and a decreased co-occupancy of histone H3K27 acetylation (mark of active enhancers) and bromodomain-containing protein 4 (BRD4) within these super-enhancers (Figure 1A) (Zhang et al., 2019). Consequently, *BRCA1* haploinsufficiency impacts long-distance chromatin interactions between targeted genes and their transcription enhancers (Zhang et al., 2019). Besides, depletion of *BRCA1* mRNA (siRNA) in MCF7 cells (Luminal mammary cells expressing estrogen receptors) led to decreased ESR1 (Oestrogen receptor locus) mRNA pool and increased R-loops accumulation within a super-enhancer upstream ESR1 locus (Chiang et al., 2019). Ectopic expression of RNaseH1 (RNA endonuclease, R-loops resolver) in MCF7 *BRCA1* depleted cells rescued the expression of ESR1 mRNA and reduced R-loops intensity within the upstream super-enhancer, indicating that *BRCA1* mediates the expression of this luminal biomarker through R-loops resolution within the upstream super-enhancer of ESR1 locus (Chiang et al., 2019). Therefore, *BRCA1* may mediate luminal differentiation (e.g., ESR1 locus induction), whereas *BRCA1* haploinsufficiency induces a basal-like transcriptome, consolidating the luminal origin of basal-like *BRCA1*-mutated breast tumors in *BRCA1* carriers.

The Tumor Suppressor BRCA1/2, Cancer Susceptibility, and Genome Instability in Ovarian Cancer

Ovarian cancer is a heterogeneous group of malignant neoplasms that differ in histological type, molecular features, and clinical behavior (deFazio et al., 2021). Histologically, 90% of ovarian cancer cases are epithelial, including serous, clear cell, endometrioid, and mucinous carcinomas (Weiss et al.,1977). High-grade serous ovarian carcinoma (HGSOC) is the most frequent (70% of cases) and the most aggressive ovarian cancer subtype (Bergstrom et al., 2017). The lack of specific biomarkers for the HGSOC subtype contributes to its poor survival rate (Bergstrom et al., 2017).

Women with *BRCA1/2* mutation carriers are 10 times more likely to develop ovarian cancer than non-carriers, which led to the use of prophylactic salpingo-oophorectomy (Surgical removal of the fallopian tubes and ovaries) to reduce the risk of ovarian cancer (Boyd et al., 2000).

Moreover, approximately 10-15% of ovarian cancer cases are attributable to *BRCA1/2* germline mutations (Pal et al., 2005; Cancer Genome Atlas Research N, 2011; Prat et al., 2005). This incidence can reach up to 90% of cases in hereditary ovarian cancers (Salehi et al., 2008). Features of *BRCA1/2*-associated ovarian carcinomas include high-grade phenotype, frequent TP53 mutations, copy number landscape features such as Cyclin-E amplification, and tumor suppressor Rb deletion (Quesada et al., 2022). P53 loss and loss of heterozygosity (LOH) play a controversial role in *BRCA1/2*-associated ovarian tumorigenesis (George and Shaw, 2014). There are mounting pieces of evidence for *BRCA1* haploinsufficiency toward several BRCA1-related functions in normal mammary tissue, which has been linked to genome instability induction, and this should also be elucidated in normal ovarian tissue (Sedic and Kuperwasser, 2016; George and Shaw, 2014). Notably, *BRCA1/2* mutations are the most prominent cause of homologous recombination deficiency (high genomic instability) in HGSOC, which improves response to platinum-based chemotherapy and PARP inhibitors (Mirza et al., 2016).

Results from patients

BRCA1/2-associated serous ovarian carcinomas showed a higher genomic instability than sporadic tumors. Besides, those *BRCA1/2*-associated tumors exhibited genome-wide loss of heterozygosity, which was associated with uniparental disomy (UPD). The UPD was detected in all analyzed *BRCA1/2*-associated ovarian tumors and only in 50% of sporadic tumors (Walsh et al., 2008). Besides, loss of heterozygosity (LOH) of the wild-type allele of *BRCA1* or *BRCA2* genes was widely observed among *BRCA1/2*-associated ovarian tumors (Maxwell et al., 2017). Notably, a study showed that the *BRCA1* LOH gene occurred within neoplastic lesions but was absent in precursor lesions of tubular epithelium, which was thought to be the origin of HGOSC. HGSOC are commonly characterized by P53 alterations, detected in 96% of cases (Cancer Genome Atlas Research N, 2011; Cole et al., 2016). Therefore, *BRCA1* LOH may be a consequence of genome instability driven by other alterations (Figure 2) (Paley et al., 2001; Salvador et al., 2008; Norquist et al., 2010). In this regard, P27 protein expression (Cell cycle inhibitor) was found to be significantly lower within P53 foci in the tubal epithelium of women harboring *BRCA1/2* mutation compared to non-carriers (Figure 2). The loss of P27 was higher in *BRCA1* mutation carriers compared to *BRCA2* carriers (Norquist et al., 2010). This result may explain the higher lifetime risk of ovarian carcinoma in *BRCA1* mutation carriers compared to *BRCA2* mutation carriers (Kuchenbaecker et al., 2017).

Besides its functions in HR repair and cell cycle control, *BRCA1* is involved in repairing oxidative DNA damage (Rodriguez et al., 2007). Indeed, the level of 8-oxoguanine (oxidative DNA damage) was significantly higher in DNA isolated from blood cells of *BRCA1* mutation carriers compared to non-carriers. This observed increase may result from a *BRCA1* haploinsufficiency in repairing oxidative DNA damages (Figure 2) (Dziaman et al., 2009). *BRCA1* mRNA levels showed lower levels in leukocytes of *BRCA1* mutation carriers compared to non-carriers (Chehade et al., 2016). Based on previous studies on *BRCA1* heterozygous human mammary epithelial cells, monoallelic alterations of the *BRCA1* gene may cause a haplotype insufficiency (haploinsufficiency) toward several *BRCA1* functions in normal ovarian cells of *BRCA1* carriers; thus, promoting genome instability and ovarian transformation (Figure 2).

Results from animal models

Mouse models with ovary Cre recombinase-mediated conditional inactivation of both *BRCA1* and/or p53 showed that the inactivation of both genes (*BRCA1* and P53) resulted in ovarian tumor formation in 54% of mice compared to only 5% with conditional inactivation of either gene alone (Quinn et al., 2009). Similarly, the knockout of *BRCA1* alone in murine ovarian surface epithelium (OSE) revealed no tumorigenesis in mice ovaries despite the development of significantly more premalignant changes (Clark-Knowles et al., 2007). These results suggest that *BRCA1* inactivation alone is not sufficient to promote mice ovarian cancer (Quinn et al., 2009).

The mechanism by which *BRCA1*-associated genomic instability progresses from non-transformed to transformed cancer cells in ovarian cancer is not entirely elucidated. Examining *BRCA1*+/- mouse genome throughout the developmental process from embryonic life to adulthood revealed structural variations, indels, and copy number variations that appear in early embryonic life and change dynamically throughout the developmental process. Indeed, numerous oncogenic genes and pathways, such as DNA damage repair, estrogen signaling, and oncogenesis found to be affected. Controversially, TP53 mutations showed limited contribution in early genome instability and are not required for *BRCA1*-driven genome instability in non-cancer cells (Wu et al., 2022). Additionally, the deletion or substitution of the *BRCA1* locus corresponding to the RING domain in mice showed a high degree of genomic instability and a defect in replication fork stability despite the accumulation of RAD51 at DNA damage sites (Figure 2) (Li et al., 2016).

Results from cell lines

BRCA1 is implicated in estrogen biosynthesis through regulating aromatase (enzyme converting androgen to estrogen) expression in ovarian granulosa cells (Hu et al., 2005). Besides, the over-expression of aromatase in mammary adipocytes (local production of estrogen) was associated with breast cancer development (Sasano and Harada, 1998). *BRCA1* knockdown (siRNA) in ovarian granulosa and pre-adipocytes cell lines showed a significant increase in aromatase expression (Figure 2). This finding suggests that *BRCA1* deficiency in estrogen-producing cells may contribute to tumor development in estrogen-responsive epithelial cells through the activation of proliferative pathways (Hu et al., 2005). In the presence of mitomycin (DNA-damaging agent), *BRCA1*-deficient primary mouse ovarian surface epithelial (OSE) cells revealed a higher number of centrosomes and a lack of Rad51 nuclear foci (Xing and Orsulic, 2006). Besides, in

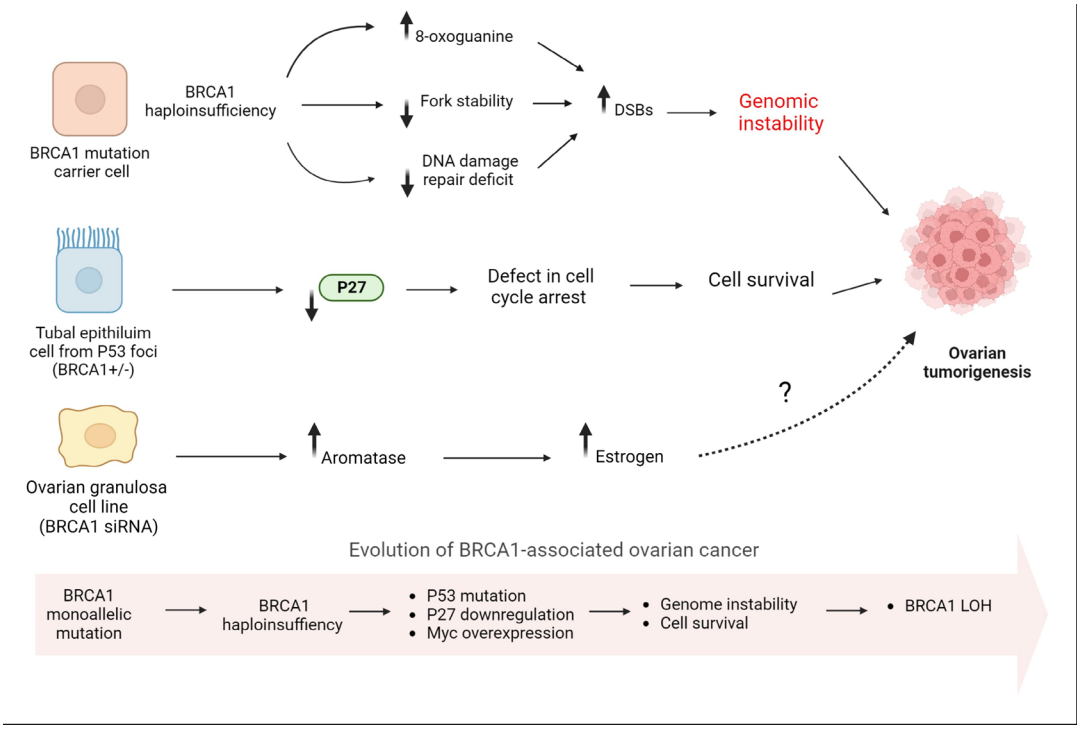

Figure 2. The Tumor Suppressor *BRCA1/2,* Cancer Susceptibility, and Genome Instability in Ovarian Cancer. *BRCA1* mutated cells isolated from *BRCA1* mutation carriers (human or mice) showed a defect in oxidative DNA damage repair (high level of 8-oxoguanine), replication fork stability, and DSBs repair, leading to DSBs accumulation and genomic instability. Tubal epithelium cells from p53 foci of heterozygous *BRCA1* mutation carriers showed a significant decrease in the expression of p27, inducing a defect in cell cycle arrest. The knockdown of the *BRCA1* gene in human ovarian granulosa cells using small interfering RNA (*BRCA1* siRNA) resulted in overexpression of aromatase, leading to increased estrogen biosynthesis. The schema at the bottom summarizes the theoretical steps of *BRCA1*-associated ovarian tumorigenesis.

those same cells, the knockout of *BRCA1* and P53 and the introduction of Myc oncogene were the minimum conditions that led to transformation (Figure 2) (Xing and Orsulic, 2006).

Bronder et al., (2021) have recently developed novel model systems of chromosomal instability (CIN) in high-grade serous ovarian cancer (HGSOC) by using CRISPR/Cas9-mediated gene editing, first to mutate TP53 and then *BRCA1* in FNE1 cells derived from non-ciliated fallopian tube epithelial cells. They demonstrated that p53 function loss was sufficient to cause subclonal karyotype alterations and global gene expression changes, affecting modules responsible for cell cycle commitment, DNA replication, G2/M checkpoint control, and mitotic spindle function (Figure 2) (Bronder et al., 2021).

The Tumor Suppressor BRCA1/2, Cancer Susceptibility, and Genome Instability in Cervical Cancer

Background

The infection with human papillomavirus (HPV) constitutes the major risk factor for cervical cancer (Bouvard et al., 2009). Indeed, HPV DNA was detected in approximately 95% of cervical malignant lesions (Waggoner and Chernicky, 2004). HPV virus was first isolated and linked to cervical cancer pathogenesis in the early 1980s (Lowndes, 2006). The genotypes of HPV that can infect the anogenital tract are classified into three groups based on their oncogenic potential: High-risk (H-R) types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) which are associated with high-grade lesions and invasive cervical cancer (Shukla et al., 2009); Low-risk (L-R) types (HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) and probably H-R types (HPV26, 53, 66) (Bouvard et al., 2009). Persistent infection with H-R carcinogenic HPV types and the integration of the HPV genome into the host chromosome of cervical epithelial cells are key early events in the neoplastic progression of cervical malignant lesions (Williams et al., 2011).

The HPV life cycle depends on the differentiation of the host keratinocytes (Longworth and Laimins, 2004). Its genome replication occurs in three phases: establishment, maintenance, and productive replication (McBride, 2017). During the first phase, HPV infects the basal layer cells of the epithelial cervix to establish the infection (Pyeon et al., 2009). Then, the viral genome is maintained at a stable number of episomes in the host cell (Anacker and Moody, 2017). Finally, the infected basal keratinocytes divide, allowing a daughter cell to keep actively dividing in the basal line while the other starts the differentiation process, favoring the productive replication of the virus (Figure 3A) (Moody and Laimins, 2010). The replication of the viral genome is only possible due to the expression of the early oncogenes E1, E2, E6, and E7 (Nilsson et al., 2018). HPV E1 and E2 are implicated directly in the viral amplification (Bergvall et al., 2013; McBride,

2013), while E6 and E7 prevent apoptosis and allow the cell cycle entrance of the host cell (Figure 3B) (Ganguly and Parihar, 2009).

To maintain the integrity of the genome, the host cell recruits several DNA repair mechanisms that can detect genomic aberrations and repair them depending on the type of damage (Nilsson et al., 2018). The two main DDR pathways are homologous recombination (HR) and non-homologous end joining (NHEJ) (Ciccia and Elledge, 2010). Double-strand DNA breaks (DSBs) require the activation of ATM, which is recruited by the MRN complex (Mre11, Rad50, and NBS1) (Ciccia and Elledge, 2010). Activated ATM phosphorylates several downstream proteins such as Chk2, NBS1, *BRCA1*, p53, and γH2AX (Matsuoka et al., 2007; Bakkenist and Kastan, 2015). On the other hand, Single strand DNA breaks (SSBs) require the activation of ATR (Zhou and Elledge, 2000) that phosphorylates downstream effectors like Chk1, RPA, and the Fanconi Anemia (FA) pathway (Shiloh and Ziv, 2013; Hollingworth and Grand, 2015).

Many studies proved that HPV exploits the DDR pathways to replicate its genome (Hong et al., 2015; Nilsson et al., 2018; Wallace, 2020). Indeed, E1 and E2 activate the DDR pathways (Bergvall et al., 2013; McBride, 2013), while E6 and E7 interfere in the counter of downstream consequences of DDR (Vande Pol and Klingelhutz, 2013; Johnson et al., 2017). DDR pathways implicated in HPV replication include key proteins such as ATM, ATR, CHK1, CHK2, H2AX, Rad51, and *BRCA1* (Figure 3B) (Sakakibara et al., 2011; Gillespie et al., 2012; Reinson et al., 2013; Chappell et al., 2016).

Cervical cancer tumorigenesis depends mainly but not only on HPV infection (Ramachandran and Dörk, 2021). The downregulation of tumor-suppressor genes in host cells contributes to the susceptibility of this cancer (de Freitas et al., 2012). Besides, based on a Swedish report, the genetic heritability of cervical cancer accounts for 27% of its risk (Magnusson et al., 2000). Many genetic association studies evaluating the risk of cervical cancer were conducted on several candidate genes implicated in cell cycle, DNA repair, and apoptosis, such as TP53 (Hu et al., 2010), E3 ubiquitin-protein ligase MDM2 (Hu et al., 2007; Hu et al., 2010), ATM (Oliveira et al., 2012), BRIP1 (Ma et al., 2013), CDKN1A (Lima et al., 2016), CDKN2A (Thakur et al., 2012) and Fanconi Anemia genes (FANCA, FANCC, and FANCL) (Juko-Pecirep et al., 2011).

Many DDR proteins with oncogenic somatic or germline mutations were considered therapeutic targets for cervical cancer, such as ATM, *BRCA1*, PALB2, and RAD51. Therefore, the use of PARP inhibitors may be beneficial for cervical cancer patients (Qiu et al., 2022). Similarly, a case-report study showed that a patient with cervical cancer, tested (due to a family history of cancer) and found positive for a pathogenic germline *BRCA1* mutation had a positive response to the treatment with bevacizumab and PARP inhibitor 'olaparib' (Montero-Macias et al., 2021).

The DNA repair genes *BRCA1* and *BRCA2* are known to increase the risk of breast and ovarian cancers (Thompson and Easton, 2002; Mersch et al., 2015). Their implication in cervical cancer is not fully elucidated.

Results from patients

Only few studies were conducted to understand the association between *BRCA1*/2 lack or loss of function and the risk of cervical cancer. A cohort study conducted on 11847 individuals from 699 different families from Europe and North America carrying a *BRCA1* mutation showed that the risk of cervical cancer was increased by 3.72 folds (95% CI = 2.26 to 6.10, P<.001) (Thompson and Easton, 2002). On the other hand, in a Swedish cohort of 1873 carriers of *BRCA1*/*2* mutations, the risk of cervical cancer was increased in *BRCA2* mutation carriers (standardized morbidity ratio (SMR) = 4.21, 95% CI =1.15±10.79, P =0.0016) while no risk was detected in *BRCA1* mutation carriers (Johannsson et al., 1999). Similarly, another study of 1072 *BRCA1* and *BRCA2* mutation carriers in the United States showed that *BRCA2* mutations slightly increased the risk of cervical cancer (Standardized incidence ratio SIR = 4.410; 95% IC = 1.61-9.599; P = 0.006) but *BRCA1* did not show any significant association with cervical cancer (Mersch et al., 2015). The increased risk of cervical cancer by both genes *BRCA1* and *BRCA2* was observed in a research on 4405 individuals from 409 carrier families (RR=4.59, 95% CI=2.20 to 8.44, and RR=3.69, 95% CI=1.20 to 8.61; p=<0.001 respectively) (Rhiem et al., 2007). Although, these studies prove the presence of a positive correlation between the increased risk of cervical cancer and at least one of the muted BRCA genes. Correspondingly, the wild-type *BRCA1* expression in cervical cancer was correlated with survival. The protein level of *BRCA1* detected using Immunohistochemistry in 70 patients showed that the survival rate within the *BRCA1*+ group was 95.5%, while it was 76.9% within the *BRCA1*- group (Paik et al., 2021).

Results from cell lines

The implicated mechanisms of cervical cancer risk in *BRCA1*/*2* carriers are not clearly established. The HPV early oncoproteins E6 and E7, known to interact with the tumor suppressor p53 and Rb1, were found to inactivate the *BRCA1* gene in cervical cancer cell lines (SiHA, Caski, and HeLa). These oncoproteins interacted directly with *BRCA1* throughout two contact points on the *BRCA1* protein, one within an N-terminal site and the other in a C-terminal region of the *BRCA1* protein (Zhang et al., 2005). Although, another research investigating the interaction of HPV oncoproteins with DDR proteins, especially homologous recombination proteins, showed that the expression of *BRCA1*, *BRCA2*, and RAD51 were slightly increased in primary human keratinocytes (HFKs) transfected with HPV16 E6 and E7. However, DSBs repair through the HR pathway was reduced by 50%, which was correlated with the mislocalization of RAD51 away from DSBs foci (Wallace et al., 2017). HPV31 E7 was also found to increase the level of many DDR proteins, including the HR proteins *BRCA1* and Rad51 (Gillespie et al., 2012; Johnson et al., 2017). Remarkably, HPV18 E2-dependent transcription was enhanced by *BRCA1* in the C33A cervical cancer cell line (Kim et al., 2003). The co-expression of *BRCA1* and HPV18-E2 was necessary for activating the E2 binding site. These proteins form a stable complex while binding through their c-terminal region.

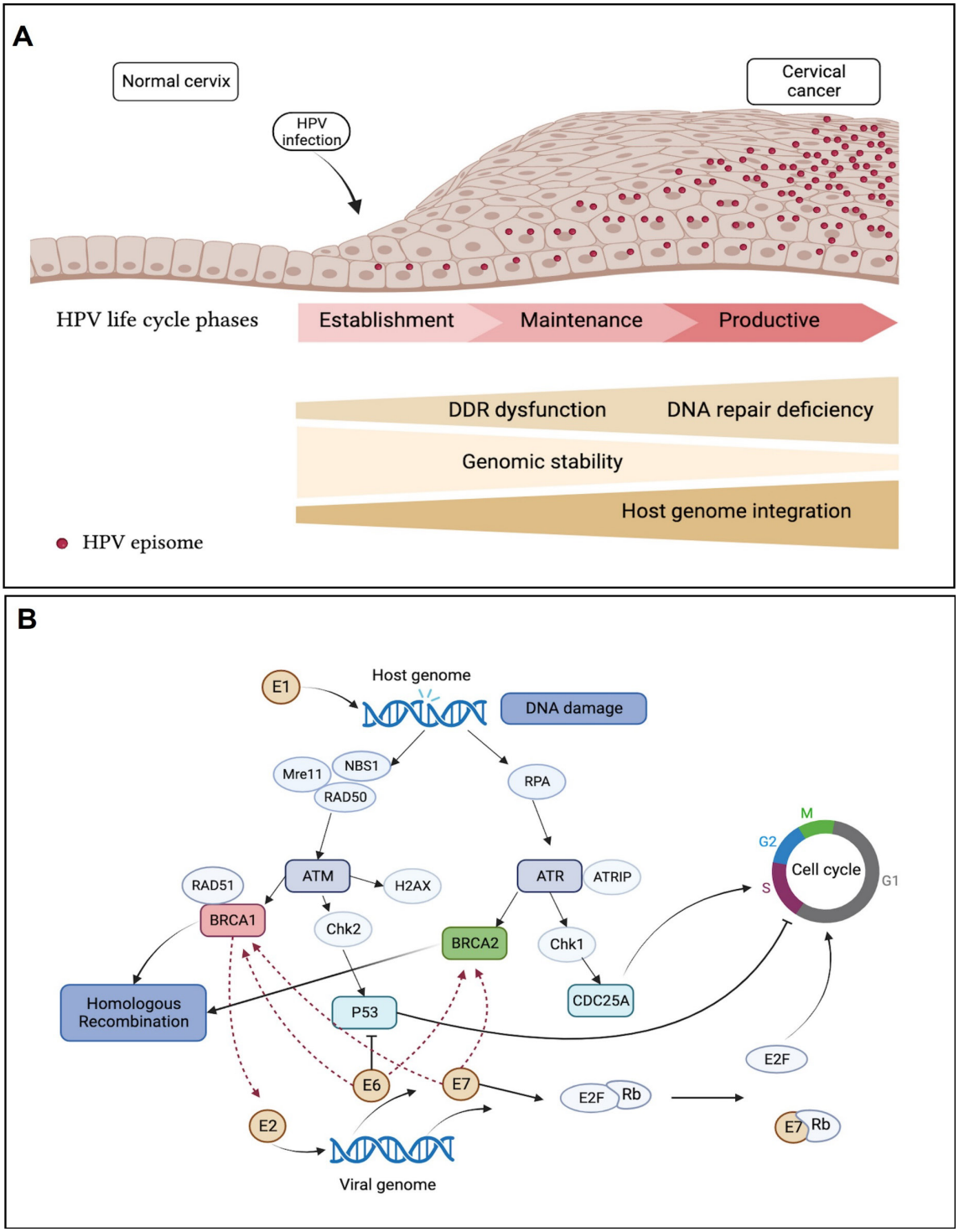

Figure 3. HPV and Genomic Instability in Cervical Cancer. **A** Model of HPV host genome integration consequences. HPV infects the cervical basal layer then starts replicating following three distinct phases (establishment, maintenance, and productive replication). During its life cycle, HPV recruits different DDR pathways and uses then in its advantage. The massive activation of the DDR pathways and the interaction of HPV oncoproteins with DDR effectors lead to the dysfunction of this mechanism. Therefore, causing a DNA repair deficiency which leads to the accumulation of DNA mutations. Furthermore, HPV integration in the host genome (e.g., chr 17q and chr 13q) leads to chromosomal aberrations. The intensity of these two phenomena, is correlated with HPV episomal copy number in the host cell. The resulting genomic instability promotes and accelerates the cervical carcinogenesis. **B** HPV oncoproteins recruit DNA damage response pathways. HPV E1 protein causes DNA damage, which activates the DDR pathway. Depending on the type of DNA damage (DSBs or SSBs), DDR leads to ATM activation via the MRN mediators (MRE11, RAD50, NSB1) and ATR activation via RPA. Once activated, these transducers lead to a signaling cascade that stimulates cell cycle arrest and the repair of the damage. In the downstream of this mechanism, E2 promotes the expression of oncoproteins E6 and E7 by hyperacetylation of the promoter region. E6 degrades p53 by ubiquitination, and E7 binds to Rb, releasing E2F and leading to the progression of the cell cycle. HPV oncoproteins also interact with BRCA1 and BRCA2 via direct protein-protein interactions. Therefore, the DNA damage remains unrepaired, and the cell escapes cell cycle arrest which allows the virus to replicate. The accumulation of unrepaired DNA damages causes genome instability and promotes cervical malignant transformation.

This study also showed that Mutant c-terminal *BRCA1* reduced the activation of E2-dependent promoter even in the presence of E2 (Kim et al., 2003). The interaction of HPV oncoproteins with *BRCA1/2* proves the manipulation of DDR pathways by the virus to promote its replication. The alteration of these pathways is well-known to promote carcinogenesis by promoting DNA mutations and genomic instabilities (O'Connor, 2015).

Furthermore, in cervical cancer, losses of heterozygosity were frequently detected within chromosome 17q (containing the *BRCA1* gene) by 44% and chromosome 13q (containing the *BRCA2* gene) by 29% (Miyai et al., 2004). Similarly, another study investigating HPV integration hotspots in the host genome showed that HPV integration was detected in 15 of 21 samples (Shen-Gunther et al., 2022). In one sample, HPV integration was detected in chromosome 17q (containing the *BRCA1* gene), while in another, HPV integration was detected in chromosome 13q (containing the *BRCA2* gene) (Shen-Gunther et al., 2022). Hence, HPV genome integration within chromosomal regions containing *BRCA1* and *BRCA2* genes may be considered as an important assist in the *BRCA1/2* associated genome instability in cervical cancer.

The mutational status of BRCA1/2 in cervical cancer is not well established. Mutation in exon 11 of the *BRCA1* gene was detected in 76% of 17 precancerous lesions of the cervix. The mutation was either a complete deletion or a deletion of one or more nucleotides (Park et al., 1999). Similarly, *BRCA1* (p.T367I) and *BRCA2* (p.Q1187fs) mutations were detected each in one sample individually in a study conducted on 10 cervical cancer tissues (Xing et al., 2018). A much larger study combining the analyses of 327 squamous cell carcinomas and 86 non-squamous cell carcinomas showed that Fanconi Anemia (FA) genes *BRCA1*, *BRCA2*, and BRIP1 were mutated in 152 patients by 3.7%, 4.0%, and 2.8%, respectively (Halle et al., 2021). In another form of genomic variability, a Chinese research investigating the genetic landscape of 64 cervical cancer samples using a validated multigene next-generation sequencing (NGS) panel revealed that *BRCA1*, *BRCA2*, ATM, and TP53 gene loci had a higher frequency of copy number variations, CNVs (Qiu et al., 2022).

Overall, *BRCA1/2* may contribute to the development of cervical cancer as a co-factor to HPV either by germline mutations (cancer susceptibility) or somatic mutations (e.g., precancerous lesions). Moreover, HPV genome integration in the *BRCA1/2* genes chromosome sites may alter their expression and thus promote genomic instability, especially in *BRCA1/2* carriers. Likewise, in cervix cells of *BRCA1/2* carriers, the possible inhibitory interaction of HPV proteins with *BRCA1* and *BRCA2* and other DDR proteins may deprive those cells of essential functions such as DSBs repair through homologous recombination pathway, thus accelerating genome instability initiated by other viral mechanisms. Indeed, the DNA repair deficiency induces the accumulation of DNA mutations and chromosomal aberrations, which plausibly promote cervical carcinogenesis (Figure 3). Further investigations are needed to clarify and decipher the implication of *BRCA1/2* genes in cervical cancer susceptibility.

Conclusions

Many studies on breast and ovarian cancers and fewer on cervical cancer investigated the link between *BRCA1/2* germline mutations and genome instability-associated tumorigenesis among carriers (Table 1). Indeed, *BRCA1/2* mutations alter various vital cellular processes, which leads to the accumulation of DNA damages, mutations of critical genes, unresolved stalled forks and R-loops, telomere dysfunction, defects in cell cycle control, and increased oxidative stress. Those alterations may cause genome instability in normal cells of *BRCA1/2* mutation carriers, leading them to transformation. Notably, *BRCA1/2* alterations are one of the main contributors to HR deficiency in breast and ovarian cancers, and they constitute determinant biomarkers for the clinical use of PARP inhibitors and platinum-derived therapy. *BRCA1/2* heterozygous human, mice, and cell lines models show immense potential in establishing the link between the haplotype insufficiency of *BRCA1/2* genes and genome instability induction. *BRCA1/2* haploinsufficiency models provide strong evidence explaining *BRCA1/2*-associated genome instability compared to the "two-hit" models that use a total silencing of *BRCA1/2* genes using siRNA in cell lines or conditional mutations in mice. In cervical and uterine cancers, the increased risk among *BRCA1/2* mutation carriers and the probable interaction of HPV with these genes, either by genome integration in their chromosomal sites or direct protein interactions, suggest an implication of *BRCA1/2* in the susceptibility of this cancer. Further investigations are needed to prove *BRCA1/2*-related HR deficiency in cervical cancer, which will promote the beneficial use of PARP inhibitors in this latter.

Overall, the poor outcome of *BRCA1/2*-associated cancers renders *BRCA1/2*-driven genome instability of substantial clinical potential. Other alterations of *BRCA1/2* genes, such as DNA methylation, are frequently observed in gynecomammary cancers and may constitute another mechanism driving genome instability that needs to be investigated, especially in sporadic disease.

Abbreviations list

ATM: Ataxia-telangiectasia mutated
ATR: ataxia telangiectasia and Rad3-related protein
BPTF: bromodomain PHD finger transcription factor
BRCA1: Breast cancer susceptibility gene/protein 1
BRCA2: Breast cancer susceptibility gene/protein 2
BRD4: bromodomain-containing protein 4
BRIP1: BRCA1 Interacting Protein 1
CDKN1A/2A: Cyclin Dependent Kinase Inhibitor 1A/2A
Chk1/2: Checkpoint kinase 1/2
CI: Confidence interval
CNV: copy number variation
DDR: DNA damage response
DNA: Deoxyribonucleic acid
DSBs: double strand breaks
ESR1: Estrogen receptor locus
FA: Fanconi anemia
FANCA/C/L: Fanconi anemia complementation group A/C/L

Table 1. Pathogenic Variants Implicated in Gynecological and Mammary Cancers: Insights from Cited Models in this Review

	Breast Models	Ovary Models	Blood Models	Uterine, Risk
BRCA1	6-KB Duplication in exon 13	6-KB Duplication in exon 13	6-KB Duplication in exon 13	5385insC, exon 19
	C61G, exon 4	L598X, exon 10	185delAG, exon 2	c.4956G>A, exon 16
	E143X, exon 6	185delAG, exon 2	1294del40, exon 10	185delAG, exon 2
	4065-4068del, exon 10	1246delA, exon 11	1323delG, exon 11	
	R1203X, exon 10	2576delC, exon 10	4446C>T, exon 12	
	R1443X, exon 12	5214C>T, exon 16	IVS8+2T>A, splice mutation implicating intron 8 and exon 8	
	185delAG, exon 2			
	943ins10, exon 10			
	1100delAT, exon10			
	1135insA, exon 10			
	2530delAG, exon 10			
	2800delAA, exon 10			
	4154delA, exon10			
	4184del4, exon 10			
	5385insC, exon 19			
BRCA2	999del5, exon 9	6174delT, exon 11		T1251fs*14, exon 11
		8765delAG, exon 20		6174delT, exon 11
		5358del4, exon 11		

Pathogenic variants associated with Breast and/or Ovarian cancer risk: findings from various models in the current review, Presented in the 'Breast Models,' 'Ovary Models,' and 'Blood Models' Columns. Founder mutations increasing the risk of breast and ovarian cancers and associated with the risk of uterine cancer are presented in the "Uterine, Risk" column. The pathogenicity (Risk of breast/ovarian cancers) and the nucleotide localization of each *BRCA1/2* variant used in different models were determined using the Clinvar database (ClinVar, 2023). Alterations with unknown significance (ClinVar, 2023) for the risk of breast and/or ovarian cancers were excluded and are not mentioned in this table. The Ashkenazi founder mutation "185delAG" is one of the most used mutations in models presented in this review. The last column, "Uterine, Risk," includes *BRCA1/2* mutations increasing the risk for uterine cancer, known as founder mutations, increasing the risk of breast and/or ovarian cancers (Laitman et al., 2019).

FOXP1: forkhead box P1
GKN: Ovarian granulosa cells
HDR: homology-directed repair
HGSOC: high grad serous ovarian carcinoma
HIS: haploinsufficiency-induced-senescence
HMECs: Human mammary epithelial cells
HPV: Human papillomavirus
H-R: High risk
HR: Homologous recombination
hTERT: human telomerase reverse transcriptase
LGRs: large genomic rearrangements
LOH: loss of heterozygosity
L-R: Low risk
MCF10A: Immortalized non-tumorigenic HMECs line
MCF7: Luminal mammary cells expressing estrogen receptors
MDM2: Mouse double minute 2 homolog
MMC: mitomycin C
Mre11: Double-strand break repair protein Mre11
MRN: Mre11, Rad50, NBS1 complex
NBS1: Nijmegen breakage syndrome 1
NHEJ: non homologous end joining
NHEJ: Non-homologous end-joining
OC: ovarian cancer
OSE: ovarian epithelium surface
P53/TP53: Tumor protein P53
PARP: poly(ADP-ribose) polymerase
pRb/Rb1: Retinoblastoma protein/ gene
PTEN: phosphatase and tensin homolog
RAD50/51: DNA repair protein RAD50/RAD51 homolog 1
RNA TERRA: Telomeric Repeat RNA
RNaseH1: RNA endonuclease, R-loops resolver
RPA: Replication Protein A
SIR: Standardized incidence ratio
siRNA: small interfering RNA
SIRT: transcriptional target of BRCA1 protein
SMR: Standardized morbidity ratio
SNU251: BRCA1 mutated ovarian cell line
SSB: Single strand break
SVs: structural variations
UPD: uniparental disomy
γH2AX: Gamma Variant histone H2AX

Author Contribution Statement

R.A.E. designed the concept and scope of the manuscript/Figures/Table, and reviewed the manuscript text. Y.B. and Z.Q. have contributed to the concept of the review, and reviewed the manuscript/Figures/Table. Y.O, F.B and F.O wrote the manuscript text and prepared Figures. Y.O. prepared Table 1.

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Not applicable for this review

Availability of data

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Conflict of interest

The authors declare no conflict of interest

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