Chapter

Quality of Life is Essential: Implications for Diagnosis and Treatment for BRCA1/2 Germline Mutations

Yuliana Sanchez Contreras, Brigney Isvettia Aceves Poveda, David Neri Acosta Gutierrez and Rosa Maria Alvarez Gomez

Abstract

BRCA1 and *BRCA2* germline pathogenic variants are a matter of concern because of their relevance in cancer risk assessment, personalized treatment options, and cancer prevention. Therefore, the study of quality of life (QoL), although complex, has been a challenge for clinical care and research implications for patients and families with hereditary breast and ovarian cancer (HBOC). This chapter aims to show the evolution of the evaluation of the QoL study according to the current needs of patients with *BRCA1/BRCA2* mutations.

Keywords: *BRCA1*, *BRCA2*, hereditary cancer, pathogenic variants, quality of life, risk-reducing surgeries, hereditary breast and ovarian cancer

1. Introduction

Since the discovery of germline pathogenic genes such as *BRCA1/BRCA2*, which confer high susceptibility to the development of cancer, medical care and research have been transformed in accordance with the needs of a group of people with an exceptional propensity for cancer. This has made it possible to speak in terms of risk management, such as clinical surveillance, risk-reducing surgeries, and targeted therapies, all aimed at a single goal, improving quality of life (QoL).

However, the term QoL, particularly in the medical field, has had several difficulties in its use, which make it even more difficult to evaluate. Although there is no homogeneous definition of QoL, particularly in chronic diseases such as cancer, survival plays an important role. Therefore, the evaluation of the QoL in non-modifiable conditions such as hereditary cancer implies an integral and multidisciplinary overview, in the spirit of not only influencing the gain of years lived in the course of a disease, or in the knowledge of the possibility of suffering from it, but also in the perception of well-being, which is a constant companion in the different moments of the processes of diagnosis, monitoring, treatment, and prevention.

2. Quality of life

The definition of QoL has had several fluctuations throughout history, all of them considered important from the point of view and context in which they have been used. This phenomenon of diversification in the definition could be explained due to socioeconomic, political, cultural, or philosophical circumstances. Consequently, it is likely that QoL is perceived differently [1]. However, we can identify two historical and crucial starting points, in which its study becomes relevant, and with it its incorporation into the medical field [2, 3]. The first dates from the mid-nineteenth century, with the dramatic increase in life expectancy in developed countries, and with chronic diseases began to play a leading role in public health [4]. This change, from acute infectious diseases to chronic diseases, also implies a change in perspective oriented to long-term treatment, which can undoubtedly increase life expectancy, but also its efficacy and cost-effectiveness [4, 5]. The second historical event begins with the incorporation of the term "Health", proposed by the World Health Organization (WHO) in 1948, which is "the complete state of physical, mental and social well-being and not merely the absence of disease" [6]. Later, in 1957, a WHO collaborating group proposed health as "a condition or quality" of a human organism, which expresses its adequate functioning under certain genetic or environmental conditions [6, 7].

With this preamble, the long road that researchers have traveled in search of a more homogeneous definition of the concept of QoL is framed. In 1966, within the framework of the World Health Forum held in Geneva, the WHO defined QoL as "the individual's perception of his or her position in life, within the cultural context and value system, in which he or she lives, and with respect to his or her goals, expectations, standards and interests" [8]. Under this precept, authors such as Andrews and Withey, focused their efforts on the study of QoL understood as "an effective response to one's own role situations or values" [9], giving way to a subjective area that should be considered in the study of QoL. Therefore, other aspects that determine certain conditions of the individual, such as economic, social, environmental, lifestyle, and even genetic aspects, should be considered in the study of QoL.

Given the complexity of the study of QoL derived from the objectives pursued in each investigation, the need arises to consider the term QoL as a construct, which should not only encompass aspects related to health, but also other aspects. At this point, several authors, including Cella et al., begin to outline two fundamental elements to be considered: a subjective component or "self-assessment", always measured from the subject's perspective; and the existence of external determinants that will potentially model this (objective component). Later, these determinants will give way to a multidimensional perspective in the study of QoL, as well as the areas or domains that should be included for a more complete assessment [10].

Among the multiple definitions of QoL that have been proposed over time, two major difficulties have become evident: a) lack of consensus or homogeneity in the definition and b) how to measure QoL [3, 11, 12].

Certainly, this problem has contributed to the use of terms such as "well-being", "Health-Related Quality of Life" (HRQoL) and even identified as "synonyms" of QoL. Thus, several authors frame the dynamic course of the study of QoL not only according to the context in which it is assessed but also from the time and area of study, considering QoL as the difference between the subject's functional level and the ideal standard [1, 10–12].

Nowadays cancer is conceptualized as a chronic disease, thanks to improvements in medical care and treatments. The study of QoL has run in parallel, seeking to better understand patients' perceptions in the spheres of physical, mental, family, and cultural health [13].

For a long time, QoL was considered as a term homologous to survival, assessing the outcome of the disease in purely numerical terms. However, it did not show the disease patient's process. Therefore, it is essential to evaluate QoL from the patient's perception, and not exclusively from the medical perspective, without losing the objective of a measurement with the aim of reducing symptoms and prolonging life [13].

In order to better understand why survival was long considered QoL, we must focus on the process of medical care received by an oncology patient, which differs from other chronic diseases. The first point is the news of the diagnosis, which involves intense emotions of shock, fear, anger, and anxiety. All of them are evoked by one word: "cancer" [14]. The second factor is "how advanced" the disease is, the clinical stage at diagnosis. This step is a crucial event since medical and surgical management will depend on its evaluation. The choice between "conservative" treatment, or the therapeutic "arsenal" of surgery-chemotherapy-radiotherapy, is a challenge for the patient, with an important emotional burden that can trigger psychiatric disorders [15].

There is ample evidence of the high frequency of anxiety and depression in cancer patients, with a frequency ranging between 10 and 20%, which is a 2 to 3 times higher risk than in the general population [16, 17]. Psychiatric symptoms triggered by the disease can negatively affect QoL [18, 19]. Therefore, Lara and collaborators [13], consider as crucial the evaluation of QoL, as part of the care before and after each intervention in cancer. Thus, QoL will fulfill its objective of being "the most sensitive and powerful measure of the results of treatments or interventions" [20] and will make it possible to identify the adaptations that each patient needs to make in the physical, psychological, family, work, social, economic and personal spheres. In this sense, the most widely used instrument in QoL, as it covers most of these aspects [21].

In this sense, it is important to consider not only the disease and its impact on the individual's health per se, but also the implications at the personal, family, and social levels, such as those faced by a vulnerable group, as the subgroup of patients who are carriers of germline variants. According to the definition of vulnerability provided by the United Nations Disaster Risk Reduction (UNDRR) in 2009, it refers to the characteristics and circumstances of a community or system that make it susceptible to the harmful effects of a hazard [22]. According to Tierney et al., the hazard is the agent or medium through which damage and loss can occur. Therefore, a definition of hazard contemplates natural, anthropogenic, and even a combination of both [22]. In this sense, the hereditary cancer group has a genetic condition, which increases their risk of suffering or developing cancer, making this non-modifiable factor an additional burden in various aspects, to manage this vulnerability, as mentioned by Kuran et al., depends in turn on access to and control of different resources. Assuming this, we cannot view vulnerability as a dichotomous aspect, since this group faces decision-making, and detailed planning to manage and adapt to long-term genetic risk [3, 23].

Considering this background, we can say that QoL as a construct should be measured from different perspectives, always contemplating the patient's ideals, as well as medical, personal, psychological, social, and even economic situations that may be involved in the modeling of the disease and that will influence QoL (**Figure 1**: Areas of quality of life assessment in patients with *BRCA1/BRCA2* germline pathogenic variants.

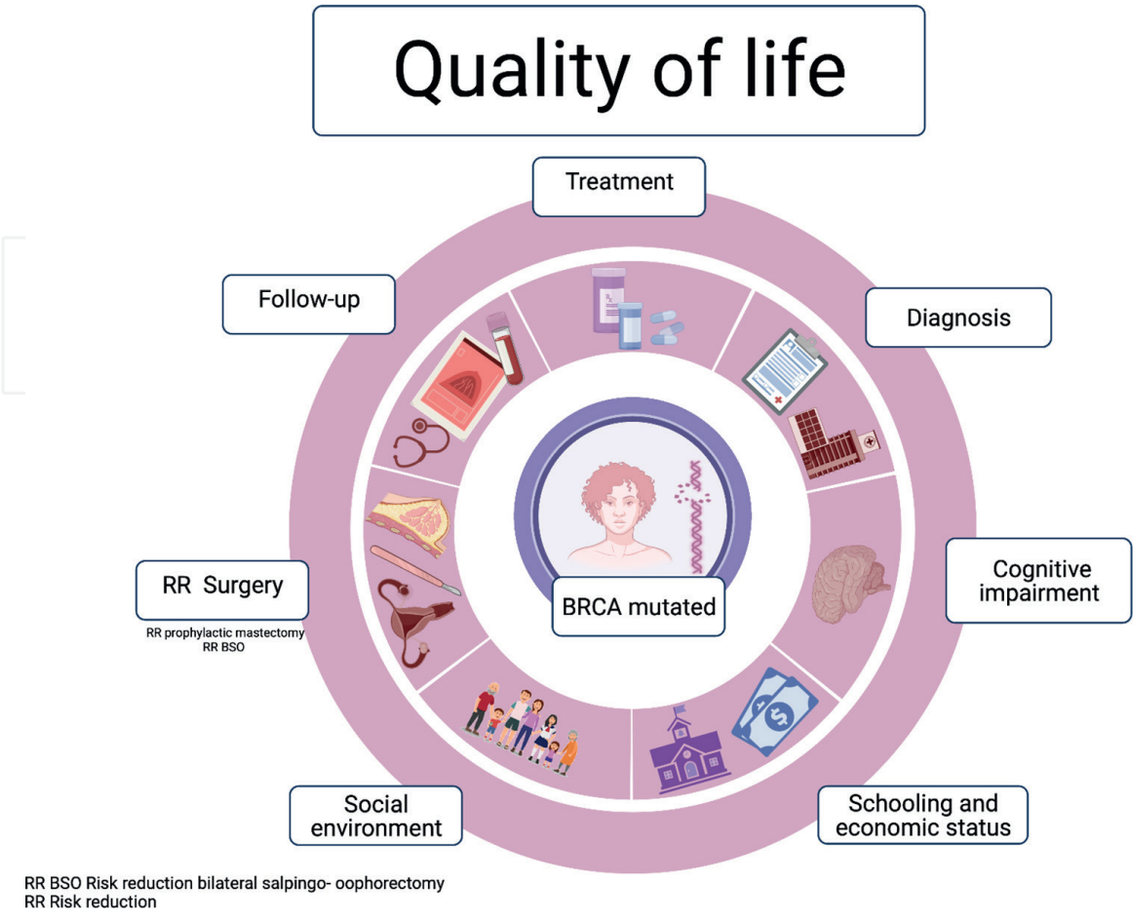

Figure 1.
Quality of life in patients that have a cancer diagnosis with BRCA genes pathogenic variants, has a meaningful repercussion in different aspects that construct life. This type of diagnosis represents a more periodic follow-up plan, including the option of risk reduction surgeries that can be a difficult decision and complex process. Adding to the previous, the possibility of inheritance to a family can increase anxiety, and have a negative impact on the patient's cognitive understanding and coping with information. All these aspects must be evaluated for a multidisciplinary assessment.

3. Quality of life in patients carrying mutations in *BRCA1 /BRCA2*

For a better understanding of the circumstances surrounding *BRCA1/BRCA2* germline pathogenic variants carriers, we need to know about the genetic context of what the term "pathogenic variant" or "mutation" implies, and why it has become a watershed for oncology, genetics, and research. In this sense, since the discovery of the cancer susceptibility related to *BRCA1* [24] and *BRCA2* [25] genes, a new perspective on conceived cancer has emerged. The BRCA genes are tumor suppressors with remarkable participation in the maintenance of genomic stability by promoting the repair of DNA double-strand breaks, by the Homologous Recombination (HR) pathway [26, 27]. The phenotype attributable, hereditary breast and ovarian cancer syndrome (HBOC), is the most studied hereditary cancer [28–30]. HBOC patients have a 60 to 80% risk of developing breast cancer, and a 16 to 45% risk of developing ovarian cancer [31–33]. Therefore, it is so important to diagnose it on time, as well as to provide care and prevention. This increased risk in this population led to the creation of groups of experts and international criteria like one of the National Comprehensive Cancer Network (NCCN), in its most recent version 2.2021 [34], which allows early identification and referral.

Research groups have directed their efforts not only to the identification of this population, but also in comprehensive care, that is, to all those areas involved in medical-psychological care (medical oncologists, surgical oncologists, geneticists, gynecologic oncologists, and oncological psychology). This comprehensive model has made evident opportunity areas with important contributions to the understanding of the health-disease process of this population, and the effect that hereditary cancer has on their QoL [33, 35, 36].

We recognize the variety of treatment schemes (surgery, chemotherapy, radiotherapy, hormone therapy, etc.) that oncology patients usually go through in their care process [37–41]. For this reason, Goerling et al. [21] state the importance of QoL study in the oncology patient, in which the different stages that the patient experiences throughout the process must be contemplated [21]. Ganz et al. describe the existence of non-medical factors that should be evaluated, such as QoL, since they have an impact on survival, and therefore should be considered as predictors of survival [42]. However, in the patient with hereditary cancer, there is an added emotional and stressful burden of knowing that she/he is a carrier of a germline variant, which increases the risk of cancer, with the possibility of being able to pass it on to offspring, a very important factor that is mostly evidenced in young women [43].

Current studies in the hereditary cancer population who undergo a genetic test, have shown increased symptoms of anxiety, depression, and stress related to the risk of suffering or developing cancer. These symptoms are even more prevalent in women who have had a cancer family history, or who have lived the experience of being the primary caregiver of a family member with cancer [43–45].

The crucial role of genetic counseling is becoming increasingly clear since it is considered a communication process for the "translation of genetic information", into words that can be understood and managed with respect to genetic risk. For this reason, the information provided not only affects the individual in question but also influences the rest of the family [46, 47].

Given this situation, it is central to emphasize the personalization of genetic counseling. According to Wenzel et al. [48], they show that people who have had personal experience of cancer have a greater adaptation to communication related to the increased risk of being a carrier, compared to the general population. However, the news given in genetic counseling are perceived with an additional psychological, emotional, social, and health load. Likewise, those women who have witnessed the death of one or more relatives because of cancer have reported greater difficulty in adjusting to the loss [48]. Thus, the QoL is significantly lower for those who have suffered the loss of a close relative, such as parents, compared to those who have not had this loss.

In addition, it is also significant to consider the "asymptomatic" state of individuals who undergo genetic testing, since it has been shown that the risk is not perceived in the same way, in comparison with those who have suffered cancer. Asymptomatic carriers perceive it as a "duality", whether they have the risk or not, and therefore decisions regarding risk management (risk-reducing surgeries or clinical surveillance), are postponed or anticipated, generating a considerable increase in anxiety, stress and anguish, and even, avoidance [48, 49].

Considering this panorama, it is essential to provide genetic counseling, so that the patient can have complete, reliable, available, and manageable information that allows them to manage the risk for their own benefit, even extending it to their family. Likewise, the emotional, psychological, and social weight of being a mutation carrier must be considered, since the environment in which the patient lives is crucial for the economic, social adaptations, and decisions [46, 48, 50].

4. Effects on quality of life in the risk care of patients carrying mutations in *BRCA1 /BRCA2*

As we have been able to appreciate, the implications of a "tiny" change in the sequence of our genetic material can cause major events in the daily life of a person. The identification of this population has made it possible to contribute to the improvement of surveillance strategies, treatments, and preventive measures, intending to reduce cancer risk and preserving life [34, 51].

The strategies will be divided into two large groups: clinical surveillance (CS) and risk-reducing surgeries (RRS). Within the first group, all those laboratory or cabinet studies that will allow surveillance of target organs are prone to the development of cancer. These studies include mammography, magnetic resonance imaging, a transvaginal ultrasound, and tumor markers, such as Ca-125 [34, 52].

For the second group, two surgical events are considered that have the purpose of removing the target organ, breasts, and/or ovaries, called risk-reducing mastectomy (RRM), in its contralateral or bilateral presentation; and risk-reducing bilateral salpingo-oophorectomy (RRBSO) [33, 53–55]. Both surgeries are cost-effective for long-term risk management [56–58].

4.1 Risk-reducing surgeries

To date, there is robust evidence of the risk reduction benefits of risk-reducing surgery, both RRM and RRBSO [59–61].

4.1.1 Risk-reducing mastectomy (RRM): contralateral or bilateral

When speaking of RRM, since 1998, there is a record of an increase in the rates of performing this surgery, a factor that possibly led to this increase was the so-called "Jolie effect" [62], in which an American actress, carrier of a *BRCA* pathogenic variant, opted for RRM. This phenomenon was widely discussed in various studies, in which the point of discussion was the pertinence of surgery, as well as the indications and the short- and long-term effects [63, 64].

Part of this evidence has made it possible to visualize that the performance of this surgery implies a reduction of at least up to 90% of the risk of developing breast cancer [33, 65]. Similarly, it has been documented the existence of medical and other factors, which may be associated with and influence the decision-making regarding its performance. These factors have been specifically described as: the accessibility to immediate breast reconstruction for aesthetic purposes; economic costs; recovery time, and the age of the patient at the time of the intervention. The average age estimated in the RRM performance was 36. 5–41 years [66], a condition that corroborates Filippo et al., stating that decision-making is more complex in premenopausal patients, among others. Likewise, this type of risk intervention had physical repercussions: infections, bleeding, lymphedema, chronic pain, and/or discomfort of the sensitive type in the surgical area, contracture, or rejection of the implant, among others [65].

As we have seen, researchers became concerned not only with the physical effects derived from the surgical procedure but also began to evaluate them from the perspective of the psychological effect [33, 67]. Among these aspects, the most evaluated were stress, depression and anxiety, all of them in relation to cancer risk, and/or the cosmetic results of risk-reducing surgery [68]. The results

obtained reveal significantly high levels of stress and anxiety perceived before surgery. However, these decreased after surgery. It is also revealed that, despite some dissatisfaction with the aesthetic results, most of the women who choose an RRM, considered themselves satisfied with the decision [33, 65, 68, 69]. Another important factor to evaluate in these studies was the effect on sexuality, obtaining results without statistically significant differences when compared with the general population [68].

It is worth mentioning that, in most of these studies, the objective has been HRQoL and not general QoL. Therefore, it is important to point out that despite the increase of RRM after the "Jolie effect", this surgery continues to be less accepted in comparison with RRBSO, since the latter is associated with a lower rate of complications, as well as a shorter recovery time [33, 65].

4.1.2 Risk-Reducing Bilateral Salpingo-Oophorectomy (RRBSO)

This surgical measure involves a reduction in the risk of ovarian cancer described in up to 95% women who are carriers of pathogenic variants in *BRCA1/BRCA2* [33, 68, 70, 71].

As with RRM, this type of intervention had to undergo several studies to demonstrate the correlation between its implementation and risk reduction [70]. This path also involved a study focused only on physical aspects or adverse events [33, 71, 72]. These studies also describe these effects and above all how they affect mostly young women [<40 years], such as early menopause, osteoporosis derived from estrogen suppression, decreased libido, and another factor of even greater concern, fertility [73, 74].

RRBSO is one of the most widely accepted risk-reducing surgeries for this at-risk population [33, 70–72]. According to the NCCN [34], this surgery is recommended in women whose parity has been satisfied, and it is also indicated in an estimated age range between 35 and 40 years [70, 71].

Among the effects described that exerted effect in areas related to HRQoL, were similar in various populations, such as shorter recovery time (if this was performed with surgical techniques that involved less invasive as laparoscopy), decreased libido, vaginal dryness, and vasomotor signs (night sweats and "hot flashes"), that would be treated with hormone replacement therapy [33, 70, 74]. Also, it has been reported, a significant increase in stress and anxiety before surgery, that decrease after the surgical event [33, 74–77].

As we have seen, both surgical events have robust evidence of their contribution to the reduction of cancer risk; however, a factor to highlight in both is the criticism of the lack of medical information describing the effects related to their performance, the times at which they should be performed, recovery times, and especially for RRM, esthetic results [33, 65]. Despite this, the acceptance rates of these forms of risk management are high in the *BRCA1/BRCA2* carrier populations [65, 70, 73]. In this sense, it is important to highlight that there is indiscriminate use of the terms QoL and HRQoL [68], as mentioned by Haraldstad et al. [1], in their systematic review on QoL research in medicine, a point of view that highlights the long road that still lies ahead in the study of QoL, and all those factors associated [1].

Razdan et al. show that although high levels of "general well-being", "body image" and HRQoL are maintained, methodological rigor must also be considered, which will allow the inclusion of other instruments that will allow the desired objectives to be achieved in the evaluation of general QoL [68].

4.2 Clinical surveillance (CV)

This type of risk management strategy involves the performance laboratories and radiological images for timely detection of cancer [33, 34, 43, 51–54, 56, 58]. Likewise, due to the "difficulty" of following patients over time, this type of study has not yielded robust evidence of a decrease in the specific risk associated, as in the case of risk-reducing surgeries. What we know today is that this type of screening involves detection in the very early stages of breast cancer specifically. However, there is a lack of studies with a close surveillance methodology for ovarian cancer [52, 78].

Particularly in this group of QoL, a significant increase in stress levels experienced by women has been documented, before medical consultation, in relation to the results of follow-up studies. [33, 34, 52]. Another non-medical aspect is the cost of surveillance studies, since these are performed regularly, and this implies an increase in expenses compared to patients who only have surveillance without adding the genetic factor, or those who opted for risk-reducing surgery. Similar data in other populations, where the RRM is less frequent, it is associated with a higher rate of surgical complications; immediate, mediate, and late, reflected as cosmetic results not well accepted by the patients [79, 80]. Other authors have evidenced the inconformity of the patients for receiving "little" information about the possible medical and cosmetic results of RRM, since by receiving more information, they would have more opportunity to weigh the complications and adversities they would face with a procedure of this nature [33, 69].

5. Quality of life: comparison between the two risk management strategies

Perhaps the question at this point is: Which care strategy is best for people with *BRCA* gene mutations, in terms of QoL? While it is true that both offer risk management, both have advantages and disadvantages. It is imperative to always consider the patient's decision. As we have seen in the first lines of this chapter, talking about QoL is not a dichotomous answer but a more complex one that allows us to contemplate factors that we do not essentially see at first glance, but that will be a fundamental part of the modeling and course of the disease, in this case, cancer surveillance and its risk management.

It is somewhat tempting to assume that one risk intervention is better than the other; however, there is evidence to support that according to the population and its context, both can be feasible options, since when both strategies were compared in different populations, the levels of QoL and HRQoL did not show a statistically significant difference [75, 76, 78]. An important fact to be highlighted in these studies comparing both strategies is the instruments used for measurement, their validation, the objectives, and, above all, the areas evaluated [1]. Likewise, it is important to consider, as mentioned by Razdan et al. the objectives and methodological strategies of each research. Therefore, talking about QoL and risk management strategies in this population is still a challenge in medical research and an area of opportunity.

6. Effects on quality of life of target therapies: PARP inhibitors for HBOC patients

Throughout the history of medicine, we have been able to corroborate the great advances that have been made in different therapies that have marked the course

of our history, from antibiotic therapy and the implementation of vaccines to the present day where a small change can be the distinction and the "target" for new therapies. Such is the case of the drugs that have caused a great revolution in oncology, the poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors (iPARP) [81, 82].

These types of therapies aim to interfere with specific molecules, block signals that favor cancer cell growth, interfere with cell cycle regulation, as well as induce cell death, preventing cancer progression [83], making them the first drugs targeting the response to DNA damage to be used in the treatment of cancer patients [81, 82] (**Figure 2**: Mechanism of action of PARP inhibitors).

Nowadays, cancer hallmarks are known such as maintaining proliferation signals, allowing cell immortality, stimulating nutrient supply to tumors, and evasion of the immune system, among others, which will allow uncontrolled and abnormal cell growth [84], therefore, anticancer drugs have been designed to target the entire panel of cancer hallmarks [81].

To date, four iPARPs, olaparib, talazoparib, rucaparib, and niraparib, have been approved by the Food and Drug Administration (FDA), and the European Medicines Agency (EMA) [81, 85] for the treatment of patients with breast, ovarian, prostate, and pancreas cancer.

These drugs have become an important axis in the treatment of patients with breast and ovarian cancer. Nevertheless, their study and effect on patients carrying mutations in genes such as *BRCA1/BRCA2* have been more relevant. Their importance lies in

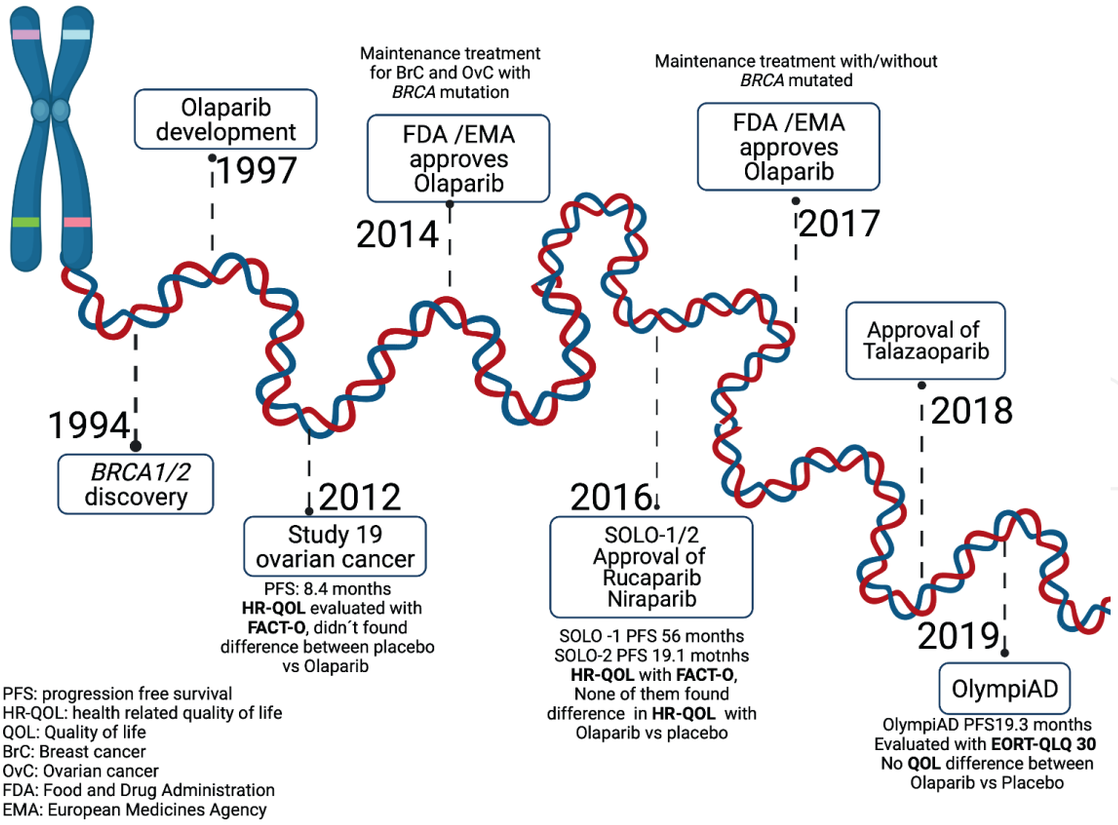

Figure 2.
(A) Normal SSBRS: PARP detects the single strand break in DNA, marking the point for the SSBRS to restore the genetic information; and (B) Olaparib treatment: Olaparib inhibits the PARP protein prolonging its repair. Eventually, the second strand of DNA will be damaged. If BRCA is mutated, the cell will be unable to repair a "double strand break", making the only way to lead to cell death.

Year	Milestone/Clinical Trial	Important events
1994	*BRCA1/2* discovery	• Association with the development of breast and ovarian cancer. (Ref)
1997	Olaparib development	
2012	Study 19	• Focus on ovarian cancer
		• PFS was significantly longer with Olaparib (8.4 months) [1].
		• HRQoL measure with FACT-O
		• No difference between placebo vs Olaparib [1].
		• Treatment with Olaparib was well tolerated and had no adverse impact on HRQoL [2].
2014	FDA/EMA approval for Olaparib	• Maintenance treatment for breast and ovarian cancer with *BRCA* mutation
2016	SOLO-1 SOLO-2	• SOLO-1 PFS was 56 months with Olaparib [3].
		• Maintenance therapy with Olaparib provided a substantial benefit to PFS [4].
		• SOLO-2 PFS was 19.1 months with Olaparib [6].
		• HRQoL with FACT-O in SOLO-2, Olaparib maintenance therapy did not have a significant detrimental effect on HRQoL compared with placebo [5].
2016	FDA approval Niraparib and Rucaparib	• Advanced ovarian cancer [8]
2017	FDA/EMA approval for Olaparib	• Maintenance treatment with/without *BRCA* mutated
2018	Approval of Talazoparib	• Germline BRCA-mutated locally advance or metastatic breast cancer
2019	OlympiAD	• PFS was 7 months versus chemotherapy treatment of physician's choice [7].
		• QoL measure with EORT-QLQ 30
		• No difference between placebo vs Olaparib

Table 1.
Important events around iPARP.

the fact that these genes, also known as "tumor suppressor", are part of a surveillance system that helps to control cell multiplication, as well as repair DNA double-strand breaks through a process known as homologous recombination (HR), thus allowing DNA integrity [81, 86]. In patients with mutations in these tumor suppressor genes, this surveillance system is affected, contributing to a key part of the action of these targeted drugs, since IPARPs disable another DNA damage repair mechanism called "PAR-ylation", achieving a break in the first DNA strand and breaking the second strand at this point in the process, However, in patients carrying pathogenic mutations in these genes, this repair process becomes almost impossible, leading the cell to what we call "synthetic lethality", i.e., it forces a highly damaged cell to imminent death to prevent its proliferation and thus perpetuate the damage [87–89].

Knowing in broad strokes the mechanism of action of these drugs, we can understand their relevance in this population. For this reason, since their discovery, several clinical trials have been carried out to determine not only their effectiveness but also the adverse effects of their administration, the doses at which they work, and, above all, the objective response rate, which refers to the reduction in tumor size after treatment, showing mostly satisfactory results in patients with *BRCA1/BRCA2* mutations [90–104].

This last factor of interest, as we have already mentioned in the first lines of this chapter, survival has been used as a synonym of HRQoL [4, 5]. Therefore, there is ample and robust evidence from clinical trials, where instruments have been used for the evaluation of HRQoL, well-being, and symptomatology, in general without obtaining statistically significant results that allow us to differentiate whether these patients carrying mutations, who benefit from a targeted therapy that increases their median progression-free survival, present optimal levels of QoL when compared with other standard therapies such as chemotherapy [105, 106].

One of the most widely used drugs today is Olaparib, which is approved by the FDA and EMA for patients with advanced ovarian cancer as maintenance therapy independent of *BRCA1/BRCA2* status [101, 102], which in clinical trials has demonstrated an increase in progression-free survival estimated at 13. 8 months to 49.9 months, compared to placebo (standard therapy) which was 5.5–19.1 months, this fact is of utmost importance to clinicians as the goal of life-sustaining is pursued. However, it has also been shown that the study of QoL in these patients and especially in this type of research, continues to be a subject to development, because HRQoL is still evaluated as a synonym of QoL, [105, 106]. **Table 1** key events in the development of PARP inhibitors and quality of life.

Likewise, this lack of an operational definition, as shown by Razdan et al. has allowed the use of various instruments that only assess HRQoL, so there is still a long way to go in this type of research, with the aim of continuing to provide better and more efficient and comprehensive medical care (**Figure 3** shows transcendent events in the history of the iPARPs).

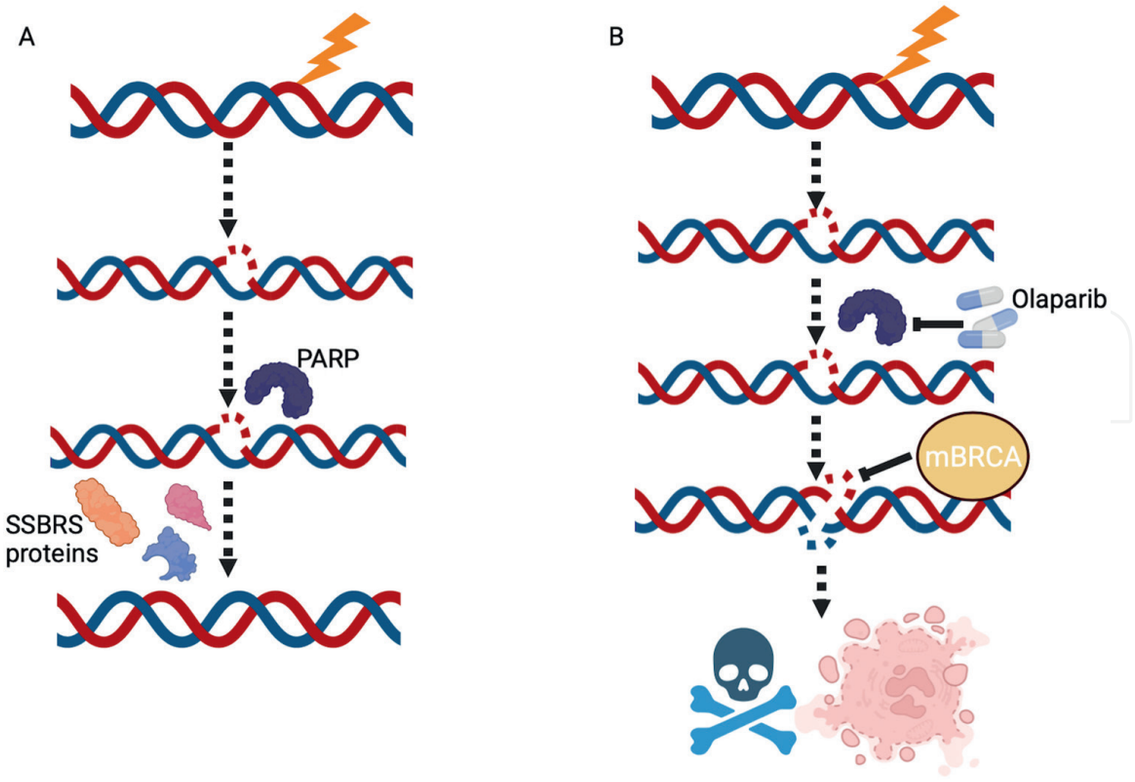

Figure 3.
This timeline represents the most important events around PARP inhibitors. From the discovery of BRCA1and BRCA2 genes and its association with the risk of developing cancer to the most relevant clinical trials that have shown an increase in the survival for this population, and how the quality of life has been evaluated in each of them.

7. Concluding remarks and perspectives

The complex concept of QoL encompasses aspects of physical, emotional, social, and cultural well-being, which may be particular to an individual. In people with increased susceptibility to cancer, for instance, carriers of germline pathogenic variants in *BRCA1* and *BRCA2* genes, the analysis of QoL presents a broad picture, involving not only the experience of cancer and its effect on one's life. It also involves family aspects, decision-making about risk reduction actions, and the perception of their repercussions, as in the case of surgeries (RRM and RRBSO).

The emergence of targeted treatments, such as PARP inhibitors, has brought to the field of the study of QoL new questions about the effects of pharmacological treatments in the context of patients with exceptional characteristics in their oncologic pathway.

As it has been pointed out by several authors in the field, it will be necessary to continue with the research of QoL in this group of patients and families, with the indispensable adaptations that will allow to dimension as broadly as possible the nature of the phenomenon.

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Conflict of interest

The authors declare no conflict of interest.

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