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Review

Radiation-induced side effects in breast cancer patients and factors affecting them

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Abstract: Breast cancer is the most frequent malignancy and the leading cause of cancer morbidity and mortality in women worldwide. Radiation therapy (RT) is a widely used approach for its treatment. About 50% of patients with malignant breast tumors receive radiation therapy and most of them appear to tolerate it, but some experience severe side effects induced by this therapy. This variability of response may be caused by several factors, like age, inflammatory responses, body weight and variation in genes involved in the response to radiation-induced DNA damage. To limit radiotherapy side effects in breast cancer patients it is therefore important to have a good knowledge of these associated factors. This review discussed about the radiotherapy-related side effects in breast cancer patients and the factors affecting them.

Keywords: breast cancer; radiation therapy; tissue damage; cardiovascular disorder; genetic makeup

1. Background

Breast cancer is the most commonly occurring cancer incidence among women and a leading factor of cancer death globally. In 2012, 1.67 million cases of breast cancer were diagnosed worldwide and were ranked as the fifth major reason of cancer death (522,000 deaths) (Youlden *et al*., 2012; Knaul *et al*., 2009).

Although the frequency of breast cancer has increased by 0.2% per year between 1997 and 2000, improvements in diagnosis and treatment have resulted in significant survival rates of breast cancer patients (Youlden *et al*., 2014). Several local therapies for breast cancer had considerably diverse effects on the length of survival and quality of life in breast cancer patients. It has long been received that RT can delay or prevent local or regional recurrence in women with early breast cancer (Roychoudhuri *et al*., 2004).

Radiotherapy is an effective treatment for breast cancer. About 50% of malignant breast tumor patients receive radiotherapy and most of them appear to tolerate it, but some experience critical side effects induced by this therapy (Borrego *et al*., 2015) (Hershman *et al*., 2006). The major side effects of radiation therapy are edema and thickness in the breast, fatigue and sunburn-like alteration in the treated area. These exchanges to the breast tissue and skin commonly go away in 6 to 12 months, and in some cases, the size of the breast becomes smaller and firmer after radiation therapy (Bovelli *et al*., 2010). Sebaceous glands and hair follicles are more sensitive to relatively low concentrations of radiation and result in the acute side effects of hair loss and skin dryness (Mathes and Alexander, 1996).

Different factors may be responsible for generating this variability, for example, age, inflammatory responses, body weight and variation in genes involved in the response to radiation-induced DNA damage (Lin *et al*., 2012). Besides, increased exposure to radiation sources and other treatment-related effects may also induce radiation associated with adverse events (Doody *et al*., 2000). This review is intended to summarize studies concerning radiotherapy-related side effects in breast cancer patients and the factors affecting them.

2. Radiotherapy

Radiotherapy (RT) is a widely used treatment in cancer. The aim of exposing the tumor to radiation is to shrink the tumor mass or to eliminate the tumor cells that may have escaped surgery. The radiation dose is calculated in gray (Gy) units, which is the amount of radiation absorbed in 1 kg tissue (Dunne *et al*., 1999). Radiotherapy can be delivered as external beam radiation or as internal radiation. Most of the patients usually receive external radiotherapy and this review will mainly focus on that.

2.1. Mechanism of radiotherapy

The major goal of RT is to deprive cancer cells of their multiplication potentially and eventually destroy the cancer cells, while minimizing exposure to normal healthy cells in the body (Lliakis, 1991). RT uses ionizing radiation for more than a century to treat cancer which is mainly based on the rationality that the rapidly proliferating cancer cells are more sensitive to radiation therapy than the normal healthy cells (Schaue and McBride, 2015).

The biological effects of RT can be resulted by the direct or indirect function of radiation on the DNA molecules. In the direct action, ionizing radiation hits the targeted DNA molecule directly, and produce DNA breaks, specifically, Double Strand Breaks (DSBs) (Mladenov *et al*., 2013). DSBs are difficult to repair and can lead to dramatic chromosomal abnormalities and genetic deletions. Therefore, DSBs increases the probability that cells will undergo cell death (Bassing and Alt, 2004). Previous studies indicated that radiation therapy like the most anticancer treatments achieve its therapeutic effect through inducing DNA damage and therefore cell death (Baskar *et al*., 2012). Several studies also found that the DNA of cancer cells repair more slowly and also develop more DNA breaks than the normal cells (Halazonetis *et al*., 2008).

Ionizing radiation can also induce indirect effects to damage DNA by generating reactive oxygen species (ROS) from water molecules of the cell (Bandyopadhyay *et al*., 1999). ROS are free radicals and mainly categorized by an unpaired electron in the structure. Therefore, they are highly reactive and can react with DNA molecules to result in molecular structural damage (Yang *et al*., 2013). ROS oxidize proteins and lipids, and induce damages to DNA, for example, generation of single-strand breaks (SSB) and apurinic/ apyrimidinic sites (abasic sites). All these changes jointly induce cell death and mitotic failure (Aparicio *et al*., 2014) (Redon *et al*., 2010).

For ionizing radiations including gamma-rays, LET X-rays, 60% of cellular damage is caused by the indirect effects (Hill, 2004). Both direct and indirect damage to DNA in the form of DNA breakage or replication stress collectively result in a complex DNA damage response (DDR). DDRs contain events that coordinate DNA repair, control of DNA replication, chromatin remodeling and apoptosis (Hershman *et al*., 2006). The ultimate result of the direct and indirect effects of RT is the biological and physiological changes that may visible in seconds or decades later.

Box 1 | Normal Tissue Tolerance

The degree of structural damage to a tissue usually depends on the cell's radio-sensitivity. The amount of ionizing radiation required to destroy the functional capability of a matured differentiated cell is much higher than that for dividing cells. The response of a tissue or organ to RT mainly depends on the cell's inherited sensitivity and also on the organization of cells in a tissue. In breast tissues, severe or grade 3 tissue damage of up to 5% is acceptable 9 (Dunne, 1999) which also accepts relatively high treatment doses. Therefore, an increased amount of toxicity of radiotherapy in case of breast cancer is acceptable to enhance the probability of cure.

3. Early side effects of radiotherapy

The early (acute) radiation reaction is a functional and morphological disorder that occurs in cells and intercellular spaces of tissues during and/or immediately after radiotherapy (Yagoda *et al*., 2009; Donnelly *et al*., 2010) (Figure 1). Acute radiation toxicity is most remarkable in tissues that renew fast, and this condition is related to the reduction of functional cells, which are removed as a part of normal tissue turnover and not replaced by damaged stem cells.

Early skin associated side effects due to RT might be considered as a sign of sensitivity toward clinical radiation. In a study with 108 patients who were treated with RT after breast surgery, the most frequent early complications identified were erythema (91.7%), moist desquamation (35.2%) and dry desquamation (29.6%). The acute side effects such as erythema and desquamation resolve rapidly without treatment (Beral *et al*., 2004). Apart from these, fatigue, lymphoedema and changes in breast color and shape are some common early symptoms after radiation therapy. RT induced early fatigue is common in up to 80% of breast cancer patients (Mohan *et al*., 2019). This early fatigue is accompanied by loss of appetite, nausea, vomiting, and of acute

radiation illness (Hickok *et al*., 2005). Lymphoedema is the swelling of the hand, arm or breast/chest area caused by a build-up of lymph fluid in the exterior tissues of the body. It can occur due to radiation-induced damage to the lymph nodes under the arm (axilla) and the surrounding area. RT after breast-conserving surgery may cause changes to the breast tissue on the treated side. So the breast may look smaller and different than before or may feel firmer (Donnelly *et al*., 2010).

4. Late side effects

Late side effects progress with time, become more severe, and generally cannot stop or reverse (Newman *et al*., 1998). The length of the latency period as hard to predict also creates a major complication for the management of patients. Moreover, the appearance of severe late radiation reactions is associated with a risk of serious complications and could permanently reduce the patient's quality of life (Bentzen, 2006) (Figure 1).

4.1. Tissue damage

Late radiation reactions, such as fibrosis, necrosis and slowly healing wounds, initiate to appear a few months after exposure and mainly reflect damage to proliferating cell fractions that are crucial for the regeneration of injured tissues (Johansson *et al*., 2000). Cells that are the progeny of exposed cells may divide and express delayed gene mutations and will bear chromosomal aberrations. This phenomenon is called radiation-induced genomic instability. It can be exposed through delayed lethal mutations (Powell *et al*., 2002) that may lead to prolonged tissue perturbation within the radiation field (Brown, 1983). According to previous *in vitro* analysis, radiation-induced genomic instability is likely to be the basis of the phenomenon of delayed lethality (delayed reproductive death, DRD) of cells (Mazurik and Mikhailov, 2004). Ionizing radiation-induced genomic instability transmitted via several generations after radiation therapy through the progeny of surviving cells (Little, 1998). Earlier studies reported that induction of delayed reproductive death or lethal mutation in many mammalian cell systems up to six generations after exposure to ionizing radiation (Suzuki *et al*., 2003). Previous *in vivo* analysis reported that radiation-induced genomic instability in hemopoietic stem cells in mouse and man occurred through ionizing radiation which could potentially contribute to leukemogenesis (Finnon *et al*., 2012).

4.2. Inflammation

Inflammation is considered as a normal biological response that is initiated after cell injury due to infection or cell damage. Growing evidence has shown that RT can modulate the immune system through the upregulation of inflammatory mediators (Di-Maggio *et al*., 2015). Particularly, the ionizing radiation-related activation of cytokine cascades is vital (Schaue *et al*., 2012). This process is called damage-induced inflammation (Candeies and Testard, 2015). Cytokine-mediated multicellular interactions initiate the fibrogenic process and vascular injury (Weintraub *et al*., 2010) which is a long-term effect of radiotherapy. Moreover, in addition to its cytotoxic activity, ionizing radiation can also trigger pro-inflammatory mechanisms in tumor and normal cells that receive sub-lethal doses, through the activation of NF-κB transcription factor. This links with carcinogenesis, inflammation and radiotherapy resistance (Schaue *et al*., 2012).

Recent experiments suggest that after radiation exposure removal of apoptotic cells enhances phagocytic cell activity and persistent macrophage activation and neutrophil infiltration. These phenomena continue even after the clearance of apoptotic bodies and may be significant determinants of the long term consequences of radiation exposure (Yu, 2012) (Chen *et al*., 2002).

4.3. Risk of second cancer

There are many pieces of evidence for the association between radiation exposure and carcinogenesis, especially from the epidemiological study of the survivors of atomic bomb irradiation (Preston *et al*., 2003; Land *et al*., 2003). It has been indicated that irradiation of surrounding tissues during breast RT can induce the chance of second cancers within these tissues (Harvey and Brinton, 1985; Neugut *et al*., 1999). From different studies radiation therapy for breast cancer is associated with the risk of developing leukemia, sarcoma, lung cancer, and esophageal cancer (Ahsan and Neugut, 1998). Generally, the latency period between exposure to radiation and the appearance of a second cancer is 10 or more years. Boice *et al.* (1987) have suggested that cancers resulting from radiation would develop after 10 years for solid tumors and within 5 years for leukemia (Zablotska *et al*., 2005).

Roychoudhuri *et al*. (2004) also found similar findings in their study. According to their observation, the risk of developing lung cancer was shown to be significantly increased in the RT cohort compared with the non-RT cohort at both 10–14 and 15 or more years after diagnosis of breast cancer. The remarkable risk of developing

myeloid leukemia was also monitored at 1 – 5 years. The risk of esophageal cancers has found significantly elevated at 15 or more years after diagnosis and RT (Roychoudhuri *et al*., 2004).

4.4. Cardiovascular disorders

Prospective studies report that after RT 50%-63% of women have experienced cardiac perfusion defects. Radiologic evidence of irreversible lung fibrosis and associated pulmonary disorders was also reported in 6 to 24 months after RT (Marks *et al*., 2000; Marks *et al*., 2005). It is here important to mention that an unhealthy lifestyle and presence of risk factors may also contribute to an elevated risk of cardiovascular disorders (CVD) in irradiated breast cancer patients. A report by Hooning *et al*. (2007) has described that 32%, 26%, 10%, and 9% of women treated with radiotherapy were smokers, had hypertension, hypercholesterolemia, and diabetes mellitus, respectively (Hooning *et al*., 2007).

Studies have shown that RT may enhance the risk of cardiovascular disease many years after initial breast cancer treatment (Batar *et al*., 2016). By observing a meta-analysis of eight randomized trials that mainly included approximately 8000 women revealed a 62% enlarged threat of cardiac death rates in women who received RT. These high rates of CVD deaths occur mainly due to high-volume irradiation to the heart that was commonly utilized in earlier RT protocols (Garcia *et al*., 2016).

Radiation-induced CVD might occur due to a mixture of both microvascular and macrovascular effects. During the microvascular level, radiation therapy leads to a decrease in capillary density which mainly declines the degree of potential collateral flow and these changes are largely subclinical. This radiation-induced altered capillary density has resulted in both rats (Zagar *et al*., 2016) and mice after larger (≥8Gy) local heart doses. This damage to the microvascular network appears to be progressive, depending on the time and dose, suggesting a greater role in the underlying cause of ischemic injury (Wang *et al*., 2007).

On a macrovascular level, RT accelerates atherosclerosis of larger blood vessels and this result can take years, or even decades to become clinically significant (Lipshultz *et al*., 2013). During the 1950s and 1960s, it was investigated that cardiac damage has resulted in radiation doses >40 Gy, whereas lower concentrations were considered to be safe (Guo *et al*., 2011). Newer RT protocols with lower radiation doses and highly focused radiation beams allow tumors to be targeted more preciously and shield the heart and other healthy tissue from the direct effect of radiation (Adams *et al*., 2003).

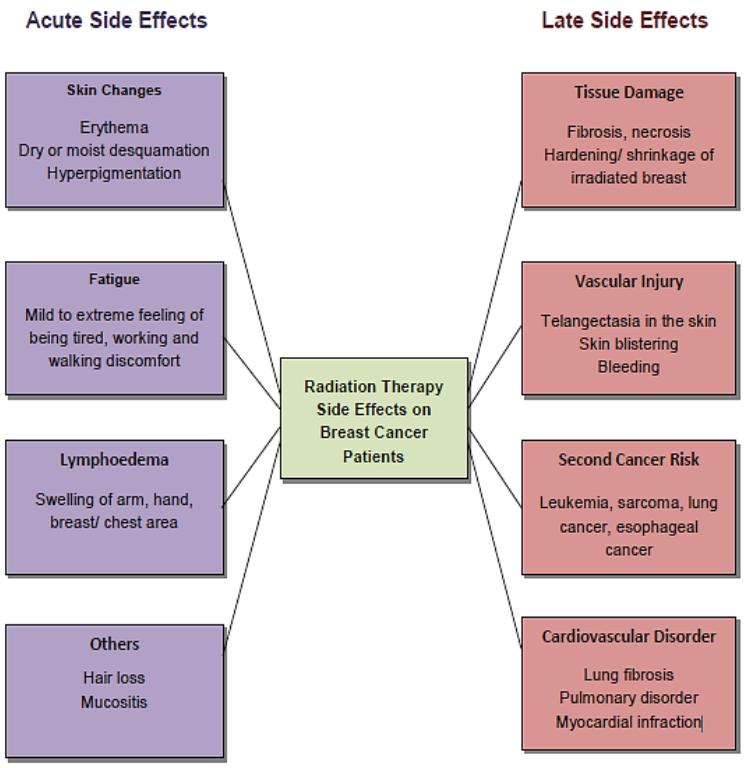

Figure 1. Acute and chronic side effects of radiation therapy on breast cancer patients.

5. Factors affecting side effects

The severity of damage to normal tissue after therapeutic RT is predominantly influenced by factors related to radiation exposure, which however are not sufficient to explain fully due to patient-to-patient variability (Turesson *et al*., 1996; Rosen *et al*., 1999). To date more than 60 publications have been published where researchers tried to identify common risk factors for RT side effects. There is significant evidence that both patient- and treatment-associated factors, as well as essential factors of individual radio sensitivity could manipulate the variability of side effects observed (Brock and Tucker, 2000) (Figure 2).

5.1. Genetic makeup

Diverse single nucleotide polymorphisms (SNPs) have been proposed to be correlated with acute or late radiation sensitivity. Genome-wide analyses showed that ionizing radiation-related SNPs are not localized in random genes but genes involved in selected processes, such as DNA damage repair, control of apoptosis, cell cycling and inflammation (Brock and Tucker, 2000; Alsner *et al*., 2008; Popanda *et al*., 2009; Rosenstein, 2011; West and Barnett, 2011).

The *BRCA1* and *BRCA2* genes were first identified and sequenced in 1994 and 1995, respectively, after analysis of high risk for breast cancer (Anglian Breast Cancer Study Group, 2000). These genes act as classic tumor suppressor genes in that only one defective copy in the germline results in cancer susceptibility but both copies are lacking in malignant cells. These genes encode large proteins, with the BRCA1 protein-containing of 1863 amino acids and the BRCA2 protein consisting of 3418 amino acids. The exact functions of these proteins are unclear, but they seem to be intimately involved in DNA repair, cell cycle control, recombination and the maintenance of genomic stability (Antoniou *et al*., 2003). According to previous studies, high complication rates occurred in women with *BRCA1/2*-associated breast cancers treated with RT (Pierce and Haffty, 2011; Smith and Isaacs, 2007). A retrospective cohort study from Pierce *et al.* (2011) reported that radiation-associated complications in 71 North American women with a *BRCA1/2* mutation with initiative stage breast cancer treated with RT. With a median follow-up of 6.75 years for *BRCA1/2* carriers and 7.75 years for controls, toxicities were comparable between these groups. The rate of breast pain was enhanced in *BRCA1/2* carriers. However, other measures of major acute toxicity (breast erythema, moist desquamation, and fatigue) were not significantly different. Late effects (rib fractures, lung fibrosis, soft-tissue/ bone necrosis, and cardiac fibrosis) were also not significantly different between carriers and controls (Pierce and Haffty, 2011).

CDKN1A (cyclin-dependent kinase inhibitor-1A) encodes p21 protein and highly active in cell cycle regulation and arrest following DNA damage and plays a crucial role in breast cancer development (Motwani and Strom, 2006). A recent study of Price *et al*. (2015) suggested that CDKN1A abnormal expression has been reported to be associated with the acute sensitivity to radiation (Price *et al*., 2015). Alsbeih *et al*. (2003) also have shown that individual response in CDKN1A is related to inherent radio-sensitivity (Alsbeih *et al*., 2003). In another study, researchers have reported an interaction between DNA damage response-related *CDKN1A* gene expression and the risk of radiotherapy-induced acute side effects (Borrego *et al*., 2015). Finnon *et al*. (2012) showed that reduced *CDKN1A* mRNA expression was associated with enhanced normal tissue radiation toxicity by comparing mild and severe acute side effects after 2 Gy irradiation of lymphocyte cultures of breast cancer patients (Finnon *et al*., 2012).

Earlier studies also resulted that *PARP1* and *XRCC1* gene expression rates were remarkably higher in control than experimental breast cancer patients. Later studies indicated that XRCC1 protein expression levels were significantly enhanced in control vs. experimental cases and higher expression of PARP1 is correlated with large tumor size (Batar *et al*., 2016). Recent studies showed that abnormal XRCC1 expression levels might be associated with the risk of radiation-induced acute side effects in breast cancer patients (Sasco *et al*., 2003). Rojo *et al*. (2012) also suggested that the over-expression of PARP1 protein was highly associated with larger tumor grade and estrogen- negative tumors formation (Rojo *et al*., 2012).

Cytokines such as transforming growth factor-beta (TGFB1), tumor necrosis factor-alpha (TNF), interferons and interleukins are also involved in the development of radiation induced-toxicity. For example, IL17 receptor knockout mice have enhanced normal tissue radiation toxicity following irradiation (Baum *et al*., 2005). Recently, a mouse model has reported substantial evidence for the role of TGFB1 in the pathogenesis of breast cancer following RT (Bentzen, 2006).

The ataxia-telangiectasia mutated (*ATM*) gene encodes a protein kinase which plays a major function in the activation of cellular responses to DNA double-strand breaks by DNA repair or apoptosis (Prokopcova *et al*., 2007). Earlier studies reported that the *ATM* gene might be responsible for up to 8% of all breast cancer cases and the loss of heterozygosity often arises in the chromosomal section 11q22–23 in breast tumors (Meyn, 1999).

Reports also showed that patients having a truncating mutation in both copies of the *ATM* gene may develop tissue toxicity if treated with RT (Mayrou *et al*., 2008).

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5.2. Body weight

Contributes to the process of wound healing, but also can lead to angiogenesis. This angiogenesis may lead to the growth of previously dormant metastatic cells (Baum *et al*., 2005). Normally, RT deteriorates the ability of cancer cells to create angiogenesis and, therefore, deteriorates the ability to metastasis. Starting RT too early after surgery may lead to the repair of this kind of radiation-induced damage and may halt the deterioration of angiogenesis.

5.3. Age

The mammary gland is highly sensitive to radiation-associated carcinogenesis, especially when exposures at young ages. The risk of contralateral breast cancer also finds higher in <45 years aged women after 10 years of receiving radiation (Fraass *et al*., 1985; Boice *et al*., 1992; Hankey *et al*., 1983). Besides this, in the case of early side effects, a higher prevalence of sleep problems and nausea is documented in younger patients after RT compared to the older patients (Hickok *et al*., 1996; Morrow, 1989).

Some previous evidence also indicated that older breast cancer patients treated with RT resulted in a lower occurrence of pain in general when compared with younger breast cancer individuals (Tesarova, 2013). Lundstedt *et al*. (2012) reported that young age is related to a greater possibility of breast pain up to 17 years after RT (Lundstedt *et al*., 2012). Gartner *et al*. (2009) from their study on 3,253 Danish breast cancer individuals found that radiotherapy at a young age was associated with a high risk of pain (Gartner *et al*., 2009). Peuckmann *et al*. also showed similar results in a study with 1,316 women. In this study, the breast cancer patients treated with RT resulted in chronic pain (duration >6 months) at different parts of the body. Besides, they accepted that RT and young age were particularly linked with a high risk of pain (Peuckmann *et al*., 2009). Furthermore, enough data indicate that age greatly influences whether a woman will result in lifelong RT-induced breast pain (Schroevers *et al*., 2006).

5.4. Involvement of other diseases

Inherited disorders such as ataxia-telangiectasia (AT) and Nijmegen breakage syndrome (NBS) are found to be associated with severe side effects of radiation, including an increased cancer risk after RT. In these disorders, the enhanced reaction to radiation could be demonstrated on the cellular level. For example, mutations in the *ATM* gene, encode a serine/threonine-protein kinase that is recruited and activated in response to DSBs and causes severe injury reactions in patients taking RT (Taylor *et al*., 1975). This indicates that rare cases of extreme sensitivity to radiation have a direct link with genetic disorders (Alsbeih *et al*., 2003; Andreassen *et al*., 2009).

6. Translational approach

From the above text, it is clear that some patients develop severe late RT induced side effects while others experience mild side effects only. It is also clear that genetic makeup helps to define a patient's radiosensitivity and is an important trigger for generating side effects. Therefore, the development of a prognostic tool to identify radiosensitive patients based on their genetic factors may allow personalized cancer treatment. Here a term is introduced called Radiogenomics, which is a genome-wide approach to characterize genetic predictors responsible for adverse radiotherapy effects. The goals of Radiogenomics are to 1) develop a predictive assay for identifying cancer patients who are most likely to develop severe radiotherapy side effects resulting from treatment with a standard RT protocol, and 2) to gather information on the molecular pathways which are responsible for radiation-induced tissue toxicities (West *et al*., 2010; West and Rosenstein, 2010). Radiogenomics studies are still in early stages; however identifying a large number of SNPs that have been replicated and validated in large, diverse cohorts may augment its chance to transit from bench to bedside (Ritchie, 2012).

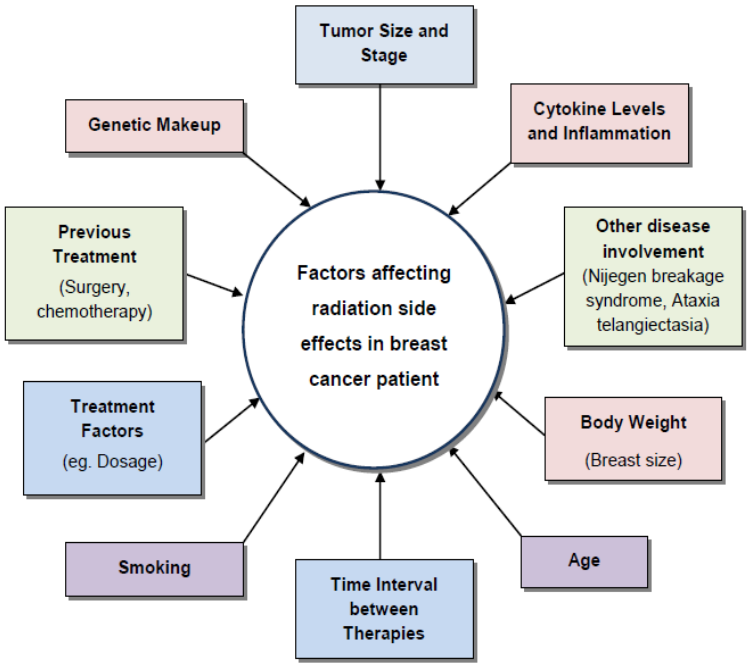

Figure 2. Factors affecting the side effects of radiation in breast cancer patients.

7. Conclusions

Breast cancer radiotherapy is associated with varying degrees of direct side effects in conjunction with significant indirect factors. During radiotherapy along with tumor cells normal tissues are also exposed to radiation. Damage of these normal tissues induces both local and systemic responses manifested by acute radiation toxicity. The risks of RT can be fully understood only after long-term follow-up studies. The factors affecting the risks of RT become increasingly important issues in the management of patients with early breast cancer. Factors associated with inflammation are characterized as major molecules for producing systemic responses to irradiation. Thus, the molecules which are directly or indirectly associated with inflammation could be used as a sensitive marker to detect exposure to radiation and monitor radiation-induced toxicity. A wide evaluation of SNPs, which is correlated with acute or late radiation sensitivity may also help to develop a useful tool for assessing breast cancer risk and also for predicting the complications related to conventional radiotherapy. In conclusion, it can be said that radiation therapies while helping in dramatic improvements in breast cancer-specific mortality, also increases the risk of side effects. It is therefore important to have a good knowledge of the radiotherapy-induced side effects and their associated factors to limit them.

Conflict of interest

None to declare.

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