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# Topical treatments to reduce severity of radiation dermatitis in breast cancer patients-a systematic review

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**ABSTRACT**

Breast cancer (BC) patients are likely to undergo radiotherapy (RT) treatment which may lead to the development of the skin toxicity, radiodermatitis (RD). The purpose of this systematic review is to evaluate the effectiveness of topical interventions in reducing the severity of RD in females BC patients. Appropriate clinical studies were independently identified through a bibliographic search in PubMed and clinicaltrials.gov. Nine randomised, controlled clinical trials (RCTs) which stated a clear inclusion and exclusion criteria, were included in this review. The studies included in this review were conducted in the last 10 years and researched the effectiveness of only topical therapies on female BC patients. The severity of RD starting at baseline 0 to endpoint was measured using the Radiation Therapy Oncology Group (RTOG) scale, and results show most patients experienced a RTOG score change of 0-1 or 0-2. A significant relationship between results obtained from 0-1 and 0-2 was shown ($p < 0.00001$). Results suggest Radioskin 1&2 cream is the most effective topical treatment for RD as 95% of patients experienced a RTOG score change of 0-1 compared to 5% experiencing 0-2. However, controlled treatments like general care and Aqua Cream seem to be the least effective, as 1.9% of patients administrating general care experienced a RTOG score change of 0-1 compared to 41.9% experiencing 0-2.

**Keywords**: Breast cancer; Radiotherapy; Radiodermatitis; Topical Treatments

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## Introduction

Breast cancer [BC] is the second most common cancer and the primary cause of death due to cancer in females worldwide, with over 2 million new BC cases in 2018 [1]. The diagnosis of BC involves mammography, Magnetic Resonance Imaging [MRI], Molecular Breast Imaging [MBI] and the most definitive method is breast biopsies [2]. Other investigation tests include immunohistochemistry to detect specific protein expression and blood-based assay using serum tumour breast biomarkers [CA 15-3, CEA and CA27-29] [2]. The treatments for BC comprise of surgical options including, lumpectomy, mastectomy or reconstruction, RT, systemic therapy involving chemo or hormonal therapy and target therapies [3]. However, the most popular approach in the management of BC is breast conservation surgery [BCS] followed by RT to minimise the risk of recurrence and ensure full recovery [2]. RT plays a vital role in managing BC and reducing recurrence rates, through destruction of subclinical diseases after surgical removal has taken place [4]. The benefits of RT should outweigh the potential side effects. Approximately, 45% of women diagnosed with BC receive RT and nearly all women experience some grade of RD, which is a very common side effect and therefore requires critical research [5].

RD is a result of the rapid formation of free radicals after RT, within the basal layer and underlying dermis [6]. RT treatment causes changes including, a decrease in the level of functional stem cells, alteration of endothelial cells and elevating levels of several cytokines and chemokines like interleukin [IL]-1$\alpha$ which is responsible skin inflammation [6]. Patients suffering from RD experience a range of symptoms including oedema [swelling], moist desquamation [thinning of the skin], ulceration, itching, dry desquamation [severe dryness] erythema [severe redness] and pain or discomfort, which are assessed by physicians using standard grading systems [7]. The severity of the RD observed by physicians vary. Radiation Therapy Oncology Group [RTOG] or Common Terminology Criteria for Adverse Events [CTCAE's] scales [Table 1] are the most common measures of the severity of RD and aid in the reproducible quantification of dermatitis [8]. Investigating the severity of RD using grading systems, provides useful information to generate effective treatment plans which may result in a better quality of life for the patient. Treatments for RD include topical corticosteroid creams, oral/topical antibiotics, or dressings [9].

Various levels of efficacy have been reported in recent research [10]. A high-quality evaluation of the effectiveness of these treatments will help patients to make informed decisions and give health care professionals valid data to base counsel of the patients on. This review will therefore focus on the change of RTOG score from a baseline 0 to endpoint whilst using particular interventions. BC patients undergoing continuous RT for the first time will be analysed. The aim of the research is to assess the effectiveness of topical treatments of RD. The treatments including creams, moisturisers, gels or ointments in reducing the severity of RD.

## Materials and methods

The electronic literature search included studies from the last 10 years. The search engines used to locate studies were PubMed and clinicaltrials.gov, however the presented trials after data extraction originated from PubMed. The search terms used were radiation dermatitis, topical treatment, and breast cancer. The Mesh descriptor for PubMed follows: [[radiation dermatitis] AND [topical treatment] AND [breast cancer]] and use of 'last 10 years' option on advanced search. A PRISMA flow chart shows the study selection process.

RCTs assessing female BC patients who received no dosage of RT prior to the study were included. Eligible trials used only the RTOG scoring system to measure the change in the severity of RD. The intervention in each RCT must be compared to a control therapy or general care. The presented studies had internal quality through control of baseline characteristics and statistical analysis showing

significance of the outcomes. Excluded studies did not meet the inclusion criteria. Extracted experiments were not RCTs and alternatively designed as case reports, retrospective, or pilot studies. There was no restriction of patient characteristics including age, health status, or prior surgical treatment of BC. The inclusiveness of the definition of participants highlights the application of the results.

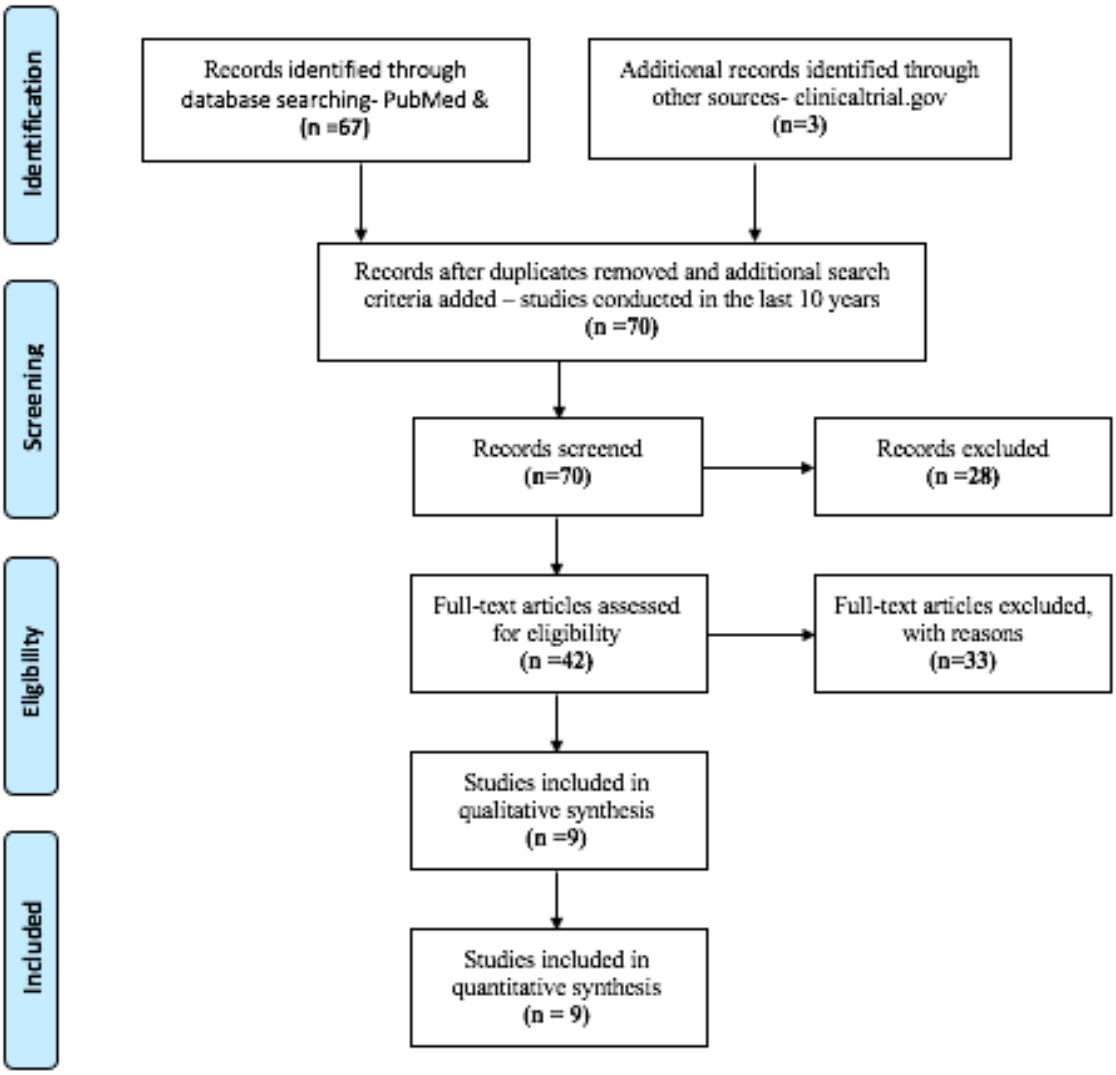



**Figure 1**: PRISMA flow chart for identification of included and excluded studies

## Results

In the nine studies included, the topical interventions assessed were: Vitamin D ointment, Aqua Cream, Topical Silver Sulfadiazine 1%, EGF-based cream, Betnovat & Essex, Essex and Canoderm, Boswellia cream, placebo cream, Neoviderm, Ixoderm, Radioskin 1&2, Xderit, Trixera+, Leviaderm, Dexpanthenol 5% and Calendula cream. In some studies, the treatment was compared to general care [11,12]. Pooling the results for the presented trials; the data consisted of 1195 participants. It was confirmed no participants had received any RT prior to the experiment, therefore baseline RTOG value is 0. However, the frequency of application of interventions differs between the trials.

RTOG scores of all participants were documented [Table 1] after completion of RT. It shows that RTOG score changes 0-1 and 0-2 are the most significant across the cohort. This outcome is supported by studies stating that most breast RD cases fall within range of Grades 1 or 2 [8]. However, the highest percentage of patients [23.5%] who developed no sign of RD when undergoing RT was witnessed when

applying Leviaderm [13]. In contrast, it is shown that a combined treatment of Essex and Canoderm cream is the least effective as 4.1% of patients were observed with a RTOG score change of 0-4 [14]. Such severe change suggests very little effectiveness of the treatment.

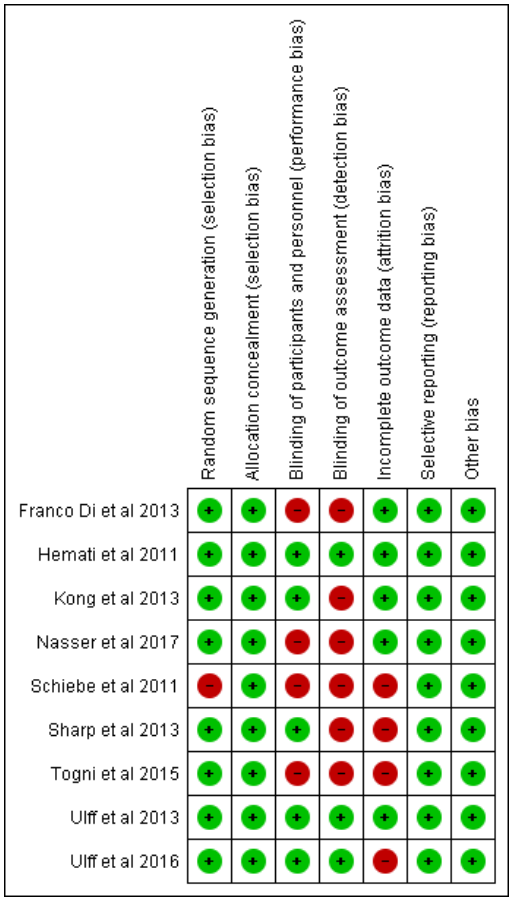
**Table 1**: The RTOG scores of all topical interventions including control from presented RCTs

| Citation | Intervention | 0 | 0-1 | 0-2 | 0-3 | 0-4 |
|---|---|---|---|---|---|---|
| Nasser *et al.* (2017) | Vitamin D Ointment | 0% | 26% | 70% | 4% | 0% |
| Nasser *et al.* (2017) | Aqua Cream | 0% | 22% | 74% | 4% | 0% |
| Hemati *et al.* (2011) | Topical Silver Sulfadiazine 1% | 0% | 15.6% | 62.7% | 21.5% | 0% |
| Hemati *et al.* (2011) | General Care | 0% | 1.9% | 45.1% | 52.9% | 0% |
| Kong *et al.* (2013) | EGF-based Cream | 0% | 30% | 55% | 15% | 0% |
| Kong *et al.* (2013) | General Care | 0% | 10% | 50% | 40% | 0% |
| Ulff *et al.* (2013) | Betnovat & Essex Cream | 1.9% | 41.5% | 43.4% | 13.2% | 0% |
| Ulff *et al.* (2013) | Essex and Canoderm Cream | 0% | 14.3% | 51% | 30.6% | 4.1% |
| Ulff *et al.* (2017) | Betnovat & Essex Cream | 10.8% | 57.8% | 23.50% | 7.8% | 0% |
| Ulff *et al.* (2017) | Essex and Canoderm Cream | 4% | 25% | 41% | 30% | 0% |
| Togni *et al.* (2015) | Boswellia Cream | 0% | 28.8% | 23.5% | 0% | 0% |
| Togni *et al.* (2015) | Placebo Cream | 0% | 45.4% | 54.5% | 0% | 0% |
| Franco Di *et al.* (2013) | Neoviderm Cream | 0% | 90% | 10% | 0% | 0% |
| Franco Di *et al.* (2013) | Ixoderm Cream | 0% | 80% | 20% | 0% | 0% |
| Franco Di *et al.* (2013) | Radioskin 1 & 2 Cream | 0% | 95% | 5% | 0% | 0% |
| Franco Di *et al.* (2013) | Xderit Cream | 0% | 20% | 40% | 25% | 0% |
| Franco Di *et al.* (2013) | Trixera+ Cream | 0% | 75% | 25% | 0% | 0% |
| Schiebe. *et al.* (2011) | Leviaderm Cream | 23.5% | 45.5% | 29% | 2% | 0% |
| Schiebe. *et al.* (2011) | Dexpanthenol 5% Cream | 2% | 16% | 54% | 28% | 0% |
| Sharp *et al.* (2013) | Calendula Cream | 3% | 71% | 19% | 3% | 0% |
| Sharp *et al.* (2013) | Essex Cream | 1% | 75% | 16% | 2% | 0% |

**Table 2**: Characteristics of included studies

| Citation | Country | Participant Size | Age Range | Surgery | Total RT Dosage | Baseline Characteristics | Study Duration | Intervention | Comparison | Application |
|---|---|---|---|---|---|---|---|---|---|---|
| Nasser *et al.* (2017) | Israel | 23 | 37-74 years (median age:63) | BCS | 50 Gy (2Gy/fraction) | Yes | 7 weeks | Vitamin D ointment-Calcipotriol | Aqua Cream | x 1 a day |
| Hemati *et al.* (2011) | Iran | 102 (51S/51GC) | mean age:48 | MRM | 50 Gy (2Gy/fraction) | Yes | 6 weeks | SSD 1% | General Care | x 3 a day |
| Kong *et al.* (2013) | Korea | 40 (20EGF/20GC) | 36-76 years (median age :56) | BCS | 50 Gy (2Gy/fraction) | Yes | 6 weeks | EGF-based Cream | General Care | x 3 a day |
| Ulff *et al.* (2013) | Sweden | 102 (53B&E/49C&E) | 28-90 years (median age: 62) | BCS OR MRM | 50 Gy (2Gy/fraction) | Yes | 7 weeks | Betnovat & Essex Cream | Canoderm & Essex Cream | x 2 a day |
| Ulff *et al.* (2017) | Sweden | 202 (102B/100E) | 27-97 years (median age: 63) | BPS OR MRM | 50 Gy (2Gy/fraction) | Yes | 7 weeks | Betamethasone-17-Valerate- Betnovat | Essex Cream | x 2 a day |
| Togni *et al.* (2015) | Italy | 114 (59B/55P) | 32-78 years (mean age 58) | BPS OR MRM | 50 Gy (2Gy/fraction) | No | Unclear | Boswellia 2% Cream (herbal) | Placebo Cream | x 2 a day |
| Franco Di *et al.* (2013) | Italy | 100 (20N/20I/20R/20X/20T) | 29-75 years (median age: 59) | BCS | 50 Gy (2Gy/fraction) | Yes | Unclear | Neoviderm, Ixoderm, Radioskin 1&2, Xderit and Trixera+ | N/A | x 2 a day |
| Schiebe. *et al.* (2011) | Germany | 101 (51L/50D) | ≥ 18 years | BCS | 50.4 Gy (1.8Gy/fraction) | No | Unclear | Silymarin-based Cream Leviaderm | Dexpanthenol 5% Cream | x 3 a day |
| Sharp *et al.* (2013) | Sweden | 411 (194C/196E) | mean age:58 | RM | 50 Gy (2Gy/fraction) | Yes | Unclear | Calendula Cream (herbal) | Essex Cream | x 2 a day |

**Table 3**: Risk of bias assessment of each study using Revman



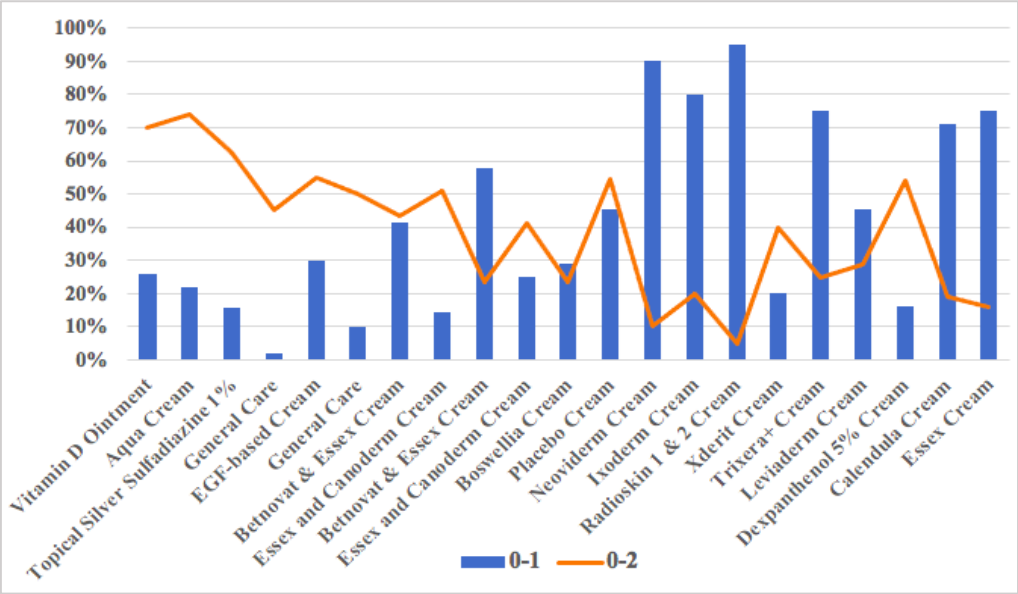




**Figure 2**: A combination graph showing the comparison between the percentage of patients experiencing a RTOG score of 0-1 and 0-2 for each intervention

The highest [95%] percentage of patients who experienced a toxicity grade change of 0-1 observed was during administration of Radioskin 1&2 cream [15] but, the controlled treatment of general care [11] resulted in the lowest percentage [1.9%] of patients with a 0-1 score change. In contrast the highest [74%] and lowest [5%] percentage of patients who experienced a RTOG score change of 0-2 was witnessed

during the application of Aqua Cream [16] and Radioskin 1&2 cream [15] respectively.

## Discussion

RD is a major concern for patients suffering from BC and receiving RT treatment. Many RCTs [Table 2] have been carried out to show topical therapies which may be appropriate management techniques to improve care. This review is based solely on the effectiveness of topical treatments and does not consider the credibility of authors. Efforts have been made to quantify the degree of skin toxicity reactions using the RTOG scoring systems, which is an excellent quantifiable method used in trials researching RD severity [8]. Alternative valid scoring systems like the CTCAE scale have been used by other authors studying RD [17]. The outcome of the trial studying the efficacy of Bemethasone and a moisturizer as topical treatments for RD in BC patients, does not correlate with the findings of the presented trials. The most significant CTCAE score change was not 0-1 or 0-2, as majority of the patients remained with no RD whilst using Bemethasone [17]. Therefore, it was important to remain consistent with the scoring system for RD, to obtain accurate results. However, some authors use non-validated scales in published articles which were extracted from our data. It is necessary to combine the results of all RCT evaluating the effect of different topical therapies in a systematic review, to establish a distinct conclusion that could be used in medical practice.

Combined results from the presented studies were documented in Table 1, showing that patients undergoing RT for the first time are most likely to receive RTOG score 1 or 2 at endpoint, however in a rare case Grade 4 was identified when applying a control treatment of Essex and Canoderm Cream [14].

There is a clear difference between the severity of each grade of the RTOG scores [18]. This confirms the need for effective topical treatment in medical practice to prevent patients from experiencing more severe and painful skin reactions as seen in RTOG score 3 or 4.

The mechanism of RD involves an interaction between an inflammatory response caused by pro-inflammatory cytokines [IL-1, IL-3, IL-5, IL-6] or chemokines and oxidative stress [19]. This implies that effective treatments of RD should have antioxidative or anti-inflammatory properties. This is evident in topical corticosteroids, like Betamethasone, which blocks inflammation by targeting cytokines such as reducing the production of IL-1 and IL-2 [19]. Recent studies confirm a statistically significant reduction in RD severity when using the corticosteroid treatment of betamethasone [$p < 0.001$] which are well-known inhibitors of skin inflammation [20]. Moreover, Table 1 shows that the highest percentage of patients experiencing a RTOG score change of 0-3 [52.9%] was observed when administrating controlled general care, which suggests this is an ineffective treatment of RD [11]. General care involves washing the area gently using mild baby soap [11]. As no anti-inflammatory agents or antioxidant are present, RD scores are more likely to worsen, which confirms the low efficacy of this treatment. Future trials should study the antioxidant and anti-inflammatory properties of interventions and state them clearly, in order to generate individually tailored treatment plans for patients. This is efficiently demonstrated in a RCT showing that a Boswellia-based cream is statistically significant in reducing the severity of RD [$0.05 < p < 0.10$]. This herbal, topical intervention contains Boswellic acids which are clearly described as having strong anti-inflammatory properties [21].

To determine effectiveness of topical therapies, combined analysis of the most significant results, RTOG scores 0-1 and 0-2, is required. Effective treatments should have a high percentage of patients experiencing a RTOG score change of 0-1, and a low percentage experiencing a RTOG score change of 0-2. This is shown when administrating Radioskin1&2 cream or Neoviderm [15]. Figure 2 shows the

relationship between the results obtained and confirms the effectiveness of the studied interventions.

Combined analysis shows that Radioskin 1&2 cream is the most effective as 95% of patients experienced maximum toxicity change of 0-1, correlating to the low percentage [5%] of patients experiencing RTOG score change of 0-2. This intervention consists of a range of agents which make up both components of the treatment: Alga Atlantica, Ethylbisiminomethylguaicolo and Manganese Cloruro [Radioskin 1], Metal Esculetina, Ginko Biloba and Aloe vera [Radioskin 2] [15]. Therefore, the results may suggest a combination of treatments within one cream could have additional effects by decreasing the likelihood of experiencing severe RD. Further research into comparing the effect of combined topical therapy as a single treatment is necessary to further confirm this inference. Also, further evaluation of herbal contents of topical therapies, like aloe vera used in Radioskin 1&2 cream, is required. Herbal treatments may have specific mechanisms of action with high or low antioxidant materials, which could enhance or reduce treatment effects of RD. A previous study has shown aloe vera gel does not significantly reduce RD as a p value of 0.06 was obtained [22]. Therefore, other herbal contents should be considered in combination treatments like Radioskin 1&2 cream, as this could enhance the positive effects of the medication. Studies have shown statistical significance [p=0.03] of Ayurvedic cream [based on sandalwood oil and turmeric] in reducing the degree of RD, as 15% of BC patients developed no signs of RD at endpoint [23].

Statistical analysis confirms a significant negative correlation between the percentage of patients experiencing a RTOG score change of 0-1 and 0-2. The relationship is shown in Figure 3.

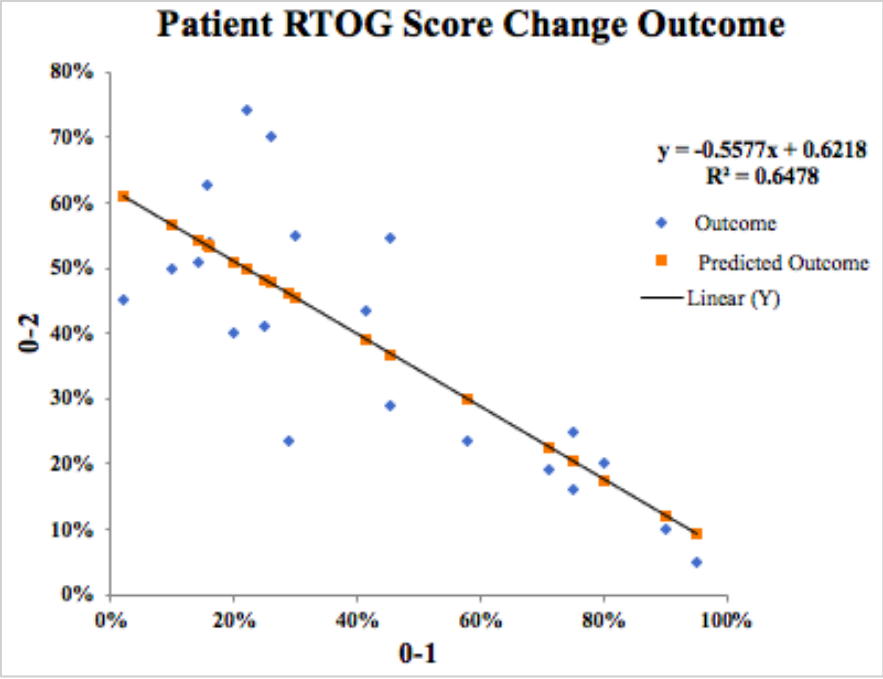



**Figure 3**: A regression model to show the relationship between RTOG score changes 0-1 and 0-2

A p-value of 6.4 x $10^{-11}$ was determined therefore, the null hypothesis is rejected as there is a very statistically significant relationship between both results. As a result, it is evident that the values did not occur by chance, providing validity to the review and confirms the use of topical interventions in current medical practice. The determined $R^2$ value [0.65] implies a good negative correlation between the two variables. Therefore, this suggests that

professionals conducting future research into this field can predict the outcome of their study. It would be possible to determine the expected percentage of patients experiencing a RTOG score change of 0-2 using the result of 0-1 or vice-versa. Therefore, this is an excellent method of providing credibility to future research.

The outcome of this review suggests that moisturisers should be considered in medical practice, as the three most effective treatments determined are, Radioskin 1&2 cream, Neoviderm and Ixoderm [15]. These moisturisers were analysed in the same RCT using the one sample of 100 BC patients from Italy who had undergone BCS. Details are provided in Table 2. Conclusions can be easily drawn as each treatment group was similarly controlled and RD was measured in the same manner, using the RTOG scale. However, the sample was divided into 5 treatment groups and patients only applied the given intervention, therefore individual differences may impact the results. Hence, a repeated study using an alternative methodology, where each patient applied all treatments on specific areas of the breast [16], may be more effective as, there will be less influence of individual differences. Another limitation is that the sample is too small and specific as only 100 Italian BC patients were included, therefore it is not possible to generalise the findings globally. As shown in Table 2, aside from this study all presented trials were not carried out on large, multi-cultural cohorts. As this review only assessed RCTs from Europe or Asia it is difficult to apply the obtained results to worldwide populations. Even though the presented trials have internal validity, as the results are applicable to the tested sample, it may not be generalised beyond that group, which could be a possible limitation. This is important as research confirms that physiological properties of the skin like, hydration levels differ between races and, these implications alter the ability of different skin types to absorb topical therapeutic agents [24]. For instance, when measuring skin moisture or hydration, Black subjects had lower skin hydration compared to Caucasians [24]. Therefore, future trials should involve patients from all racial backgrounds to reduce the effect of extenuating factors.

A previous systematic review studies the topical management of RD in BC patients [25]. There are limitations with this review as included studies used different tools in measuring RD, leading to differences in outcomes reported. Therefore, the current systematic review was designed to overcome this limitation and focus specifically on studies which used RTOG scoring scale, to minimise the effect of bias. Moreover, all patients began at a baseline of 0 and received no RT before the study began to ensure a clear RTOG score change can be observed. In contrast, a recent study evaluating the effectiveness of Epigallocatechin-3-gallate [EGCG] as a topical therapy for RD in breast cancer patients shows that 71.4% of patients with a baseline RTOG score of 1 remain at 1 once undergoing the treatment [26]. Therefore, this confirms that topical interventions are effective methods in preventing the severity of RD, however more research is required to ensure whether treatment is most effective when applied to patients with no RD or when patients develop Grade 1 dermatitis. There are limited studies available using the baseline RTOG value 1.

In addition, the presented studies were not controlled for basic characteristics, including prior surgical treatment of BC, study duration and application of intervention [Table 2]. Some studies had a specific inclusion criterion, that only females who had undergone BCS [12,13,15,16] or radical mastectomy [RM] [11,27] were included. However, other presented studies did not control this factor, as BC patients either had BCS or modified RM [13,16,21]. This can be seen as an extenuating factor, as each female may experience different surgical effects which could interfere with the performance of the given intervention. The presented studies all provided a clear inclusion and exclusion criteria which is

essential from high-quality research, in order to achieve a suitable sample. Also, Table 2 indicates that most presented studies included baseline participant data to minimise the effect of extraneous variables like BMI, age, or brassiere cup size. As the baseline characteristics of each study populations were not controlled in this review, future studies should control this in order to minimise effects of other factors on the results.

Moreover, further research into how topical interventions improve symptoms of RD including, moist desquamation and pain is essential. Adverse of effect of RD can be assessed using Visual Analogue Scales [28]. A RCT investigated the number of days it took patients to develop a RTOG score of 2 and the occurrence of moist desquamation [29]. Results showed that the medicinal plant extract gel, Nigella Sativa L. 5%, significantly delayed incidence rate of RTOG Grade 2 and reduced the severity of moist desquamation [29]. Therefore, this supports the findings of this review and suggests further studies should consider comparing changes in symptoms alongside RD severity, to improve the quality of life of patients.

## Conclusion

This review concluded that most topical interventions are effective in reducing the severity of RD. Therefore, this confirms the use of topical treatments in medical practice. The results indicate the most significant RTOG score changes observed were 0-1 and 0-2, and a good negative correlation is shown between the obtained values for both. In conclusion, the most effective intervention studied is Radioskin 1&2 cream compared to general care as the least effective. Future studies should address adverse effects of RD including pain or moist desquamation and control administration of the agents as each patient should apply all studied treatments.

## Declarations

### Ethical approval and consent to participate

The faculty research ethics committee waived the need for ethics approval and the need to obtain consent for the collection, analysis and publication of this systematic review and meta-analysis

### Consent for publication

Not applicable

### Availability of data and materials

All data generated or analysed during this study are available from the corresponding author on request.

### Competing interests

The authors declare that they have no competing interests

### Funding

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### Authors' contribution

RB contributed to the literature search, data extraction, analysis of the results and writing of the manuscript. BI designed and directed the systematic review, confirmed accuracy of the literature searches and data interpretation, and revised the manuscript critically for intellectual content. All authors approved the version of the manuscript to be published.

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Not applicable

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