The relationship between post-surgery infection and breast cancer recurrence

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SUMMARY

Breast cancer is the second most prevalent form of cancer in women worldwide, with surgery remaining the standard treatment. The adverse impact of the surgery remains controversial. It has been suggested that systemic factors during the postoperative period may increase the risk of recurrence, specifically surgical site infection (SSI). The aim of this review was to critically appraise current published literature regarding the influence of SSIs, after primary breast cancer surgery, on breast cancer recurrence, and to delve into potential links between these. This systematic review adopted two approaches: to identify the incidence rates and risk factors related to SSI after primary breast cancer surgery; and, secondly, to examine breast cancer recurrence following SSI occurrence. Ninety-nine studies with 484,605 patients were eligible in the SSI-focused searches, and 53 studies with 17,569 patients for recurrence-focused. There was a 13.07% mean incidence of SSI. Six-hundred and thirty-eight Gram-positive and 442 Gram-negative isolates were identified, with methicillin-susceptible Staphylococcus aureus and Escherichia coli most commonly identified. There were 2077 cases of recurrence (11.8%), with 563 cases of local recurrence, 1186 cases of distant and 25 cases which recurred both locally and distantly. Five studies investigated the association between SSI and breast cancer recurrence with three concluding that an association did exist. In conclusion, there is association between SSI and adverse cancer outcomes, but the cellular link between them remains elusive. Confounding factors of retrospective study design, surgery type and SSI definition make results challenging to compare and interpret. A standardized prospective study with appropriate statistical power is justified.

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Breast surgery

Introduction

Predominantly a disease that presents in females, breast cancer has been identified as the most commonly diagnosed form of cancer in women globally, with an estimated 2 million reported cases a year [1]. Breast cancer for the most part is a treatable disease, with the survival rate improving due to
enhancements in screening and treatment [2]. However, cancer recurrence remains a dominant contributor to breast-cancer-related deaths. Specifically, this is when a sub-population of primary tumour cells acquire genetic and epigenetic changes and may either persist as dormant or spread systemically, evading treatment, and facilitating relapse months or years later. When breast cancer recurs, the 5-year survival rate can drop from 70—80% to less than 30% [3]. Breast cancer recurrence can occur as either local recurrence (LR), at the same site, or as distant recurrence (DR), metastasis to a different anatomical site, or both. The risk of 10-year recurrence varies depending on cancer subtype and adjuvant therapy, but has been found to range from 4% to 34% [4].

Surgery remains the standard treatment for breast cancer. However, the adverse impact of surgery remains controversial, although not yet fully understood. It has been suggested that the change in tissue and tumour microenvironment (TME) caused by the surgery may alter the growth kinetics of breast cancer cells [5]. Surgical site infections (SSIs) have been shown to be the leading cause of operation-related adverse events [6,7]. They represent a significant issue that can reduce the quality of life and prognosis of patients following surgery, as well as increase the financial burden to patients, hospitals and

A

![PRISMA flow diagram](image-url)

Figure 1. PRISMA flow diagram of search results focused on: (a) surgical site infection after primary breast cancer surgery and (b) surgical site infection and recurrence after primary breast cancer surgery.
Breast surgery is classified as a clean surgical procedure, with no exposure of the respiratory, alimentary or genito-urinary tracts. As such, the expected rate of SSI incidence in the postoperative period is approximately 1–3% \[9\]. However, studies examining this have found that this approximation does not hold up in practice, suggesting that such procedures should be treated as clean-contaminated. Previous systematic literature reviews found that the use of antibiotic prophylaxis, not normally required for clean surgeries, reduces the likelihood of obtaining an SSI \[10\]. Indeed, breast cancer may be a key variable associated with SSI. Infection rates are higher in patients with breast cancer when compared with non-cancer patients who undergo similarly extensive operations, such as breast enhancement surgery \[11\]. Recent studies have also demonstrated that the breast tumour microbiome is distinctly different than that of the normal breast tissue, with a more rich and diverse bacterial load. Interestingly, they also demonstrated that breast tumours have larger and more diverse microbiomes than any other tumours they examined \[12\].

The progression, treatment and prognosis of breast cancer is influenced considerably by the TME. The TME in breast cancer is a complex structure comprising of stromal cells, including fibroblasts, mesenchymal stromal cells, osteoblasts, adipocytes and pericytes as well as non-stromal cells, such as the extracellular matrix (ECM) and immune cells \[13,14\]. Disturbances of the TME, such as SSI at the time of primary surgery, have been correlated with breast cancer recurrence \[15,16\], but the mechanisms mediating this phenomenon have...
yet to be elucidated. Theoretically, infections may promote a local immune-derived anti-tumour response. Bacterial infection may potentially stimulate the host's natural killer cells and macrophages, inducing a strong anti-tumour immune response protecting against invading pathogens and transformed cells, including cancer cells [17]. Conversely, it has been suggested that, as acute infections stimulate local levels of cytokines, growth factors, and proteinases, these may in turn alter the TME to support tumorigenesis. Breast cancer cells, influenced by their microenvironment, 'hack' the tumour promoting cancer-associated fibroblasts and cytokines, increasing proliferation, migration and invasion [18,19].

Table I
Demographic information summaries for the two search topics included in this review

<table>
<thead>
<tr>
<th></th>
<th>SSI</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (N)</td>
<td>99</td>
<td>53</td>
</tr>
<tr>
<td>Participants (N)</td>
<td>484605</td>
<td>17569</td>
</tr>
<tr>
<td>Countries (N)</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Period of data collection (years)</td>
<td>1980–2018</td>
<td>1989–2017</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.6 (±7.3)</td>
<td>53 (±7.1)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>17 (±26)</td>
<td>51 (±25)</td>
</tr>
<tr>
<td>SSI (%)</td>
<td>13.07</td>
<td>6.8</td>
</tr>
<tr>
<td>Recurrence (N)</td>
<td>338</td>
<td>2077</td>
</tr>
<tr>
<td>Main study type</td>
<td>Retrospective</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Main surgery type</td>
<td>Varied</td>
<td>Varied</td>
</tr>
</tbody>
</table>

The second aim was to examine cases of breast cancer recurrence following primary breast cancer surgery, where occurrence of SSIs were also recorded, and to delve into potential links between these two events.

Methods

Search strategy

This review protocol was designed according to PRISMA guidelines [20]. The electronic databases Web of Science (1990–2020), PubMed (1950–2020), CINAHL (1961–2020), Science Direct (1997–2020), Embase (1947–2020), Cochrane (1993–2020) and Medline (1879–2020) were searched up to March 2020, using the terms listed below, combined with Boolean operators, in the title or abstract.

The first group of searches focused on SSIs after primary breast cancer surgery using the keywords "Breast" "Infection" "SSI" "surg*" "Cancer" or "tumor" or "tumour" "microbiol*". For example: ("Breast" AND ("Infection" OR "Surgical Site Infection" OR "SSI") AND ("Cancer" OR "Tumor" OR "Tumour") AND "Microbiology").ab,ti.

The second group of searches focused on breast cancer recurrence following primary breast cancer surgery, where occurrence of SSIs was also recorded, using the keywords "Breast" "Cancer" or "Tumor" "Infection" "SSI" "Surgery" "Recurrence". For example: ("Breast" AND ("Infection" OR "Surgical Site Infection" OR "SSI") AND ("Cancer" OR "Tumor" OR "Tumour") AND "Recurrence").ab,ti.

Inclusion criteria

Searches were limited to articles published in the English language in a peer-reviewed journal only, with no specific year limit. Articles found using the search terms, combined with Boolean phrases, were assessed for eligibility. All articles were imported to EndNote reference manager (Endnote X8) and screened firstly based on title/abstract, and, if potentially eligible, a more in-depth analysis of full text. Articles were excluded if they were not available in English; if the patients had not undergone primary breast cancer surgery; if they did not involve breast cancer patients; if there was no mention of infection or wound healing; and/or if they were protocol papers or conference abstracts.

Data extraction

The study characteristics were extracted into Microsoft Excel. These included study details, such as: location and type of study; patient demographics; surgery type; length of follow-
up; and SSI details including number of SSIs that developed, where they developed, causative pathogens and what definition was used to classify the infections. Secondary outcomes were also recorded: number of postoperative complications, cancer recurrence, smoking status and body mass index (BMI). Graphs and figures were created using GraphPad Prism 8 (GraphPad Software, Inc.).

### Results

#### Literature search

Following examination of full texts and application of appropriate exclusion based on the aforementioned criteria, searches that focused on SSI characteristics following primary breast cancer surgery yielded 899 studies, of which 99 [21–60] [61–100] [101–119] were eventually included in this arm of the review. For the cancer recurrence focused search, 554 papers were screened and 44 [15,16,23,59,78,82,93,104], [22,33,95,120–152] were included in the data extraction, as depicted in Figure 1. The screen also identified two systematic reviews [153,154] from which nine papers were found to be eligible for inclusion [155–163]. In total, for the SSI arm, data

![Figure 2](image-url)

**Figure 2.** (a) Mean incidence of surgical site infection (SSI) in the 99 papers included in the SSI section of this study, including comparison of rates according to length of follow-up period. Error bars represent standard deviation. (b). Characterization of bacteria isolated from breast surgical wounds following breast cancer surgery. (c) Bacterial species identified from breast surgical wounds following breast cancer surgery.

#### Table IV

<table>
<thead>
<tr>
<th>Definition of SSI</th>
<th>SSI N</th>
<th>SSI %</th>
<th>Recurrence N</th>
<th>Recurrence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not defined</td>
<td>45</td>
<td>45</td>
<td>49</td>
<td>92</td>
</tr>
<tr>
<td>Own criteria</td>
<td>18</td>
<td>18</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>CDC</td>
<td>24</td>
<td>24</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NSQIP</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Asepsis score</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Culture positive</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CDC, Centres for Disease Control and preventions; NSQIP, National Surgical Quality Improvement Program.
were extracted from 484,605 patients in the 99 studies across 29 countries with 127 different outcomes recorded. Data from 17,569 patients were extracted from across 20 countries with 56 different outcomes recorded in the recurrence arm, as summarized in Table I. All patients were breast cancer patients analysed following their primary cancer surgery.

**Type of study**

Over 50% of the studies in the SSI arm of this review and over 65% of the recurrence studies used a retrospective study design, as demonstrated in Table II. This involves screening and extracting data from hospital charts of patients who had undergone breast cancer surgery previously.

**Characterization of included surgery types**

The majority of the studies did not classify their results according to surgery type, pooling all breast cancer surgeries together (Table III). Of those that did so, mastectomy was the most common. These were further classified into total mastectomy \((N = 111,931)\), partial mastectomy \((N = 52,723)\), mastectomy followed by either immediate \((N = 6178)\) or delayed reconstruction \((N = 4279)\) and modified radical mastectomy \((N = 459)\). The category of surgery is an important aspect when considering SSI, as there are multiple operative factors such as surgical technique, surgery duration, disruption to lymphatic drainage and neoadjuvant therapy that may influence the likelihood of an infection.

**Definition of SSI**

A total of 14,455 cases of SSI were recorded from the 484,605 patients included in the SSI focused segment of this review (2.98%). This ranged from 0.2% to 84.6%, with a mean incidence of 13.07% (Figure 2a). Seventeen \([31,41,43,44,53,55,72,76,86-88,91,110-113,117]\) papers recorded the culture results of the SSIs. Identification of the causative bacterial species determined involvement of 638 Gram-positive and 442 Gram-negative isolates, as depicted in Figure 2b. The most common causative bacteria identified were meticillin-susceptible *Staphylococcus aureus* (MSSA), responsible for 26% of the SSIs, *Escherichia coli* found in 20%, followed by unspecified *S. aureus* strains (19%), *Pseudomonas aeruginosa* (9%), meticillin-resistant *S. aureus* (MRSA) (6%), *Enterobacter cloacae* (4%) and *S. epidermis* (4%), as illustrated in Figure 2c.

### Table V

**Association between infection and breast cancer recurrence**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample (N)</th>
<th>Recurrence N (%)</th>
<th>Infection N (%)</th>
<th>Infection &amp; recurrence (N)</th>
<th>Follow-up (months)</th>
<th>Statistical association found?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdullah et al., 2019 [23]</td>
<td>Ireland</td>
<td>Retrospective</td>
<td>107</td>
<td>8 (7.5%)</td>
<td>19 (17.8%)</td>
<td>1</td>
<td>47</td>
<td>×</td>
</tr>
<tr>
<td>Beecher et al., 2016 [15]</td>
<td>Ireland</td>
<td>Retrospective</td>
<td>229</td>
<td>44 (19.2%)</td>
<td>44 (19.2%)</td>
<td>24</td>
<td>80</td>
<td>v</td>
</tr>
<tr>
<td>Indelicato et al., 2007 [59]</td>
<td>USA</td>
<td>Retrospective</td>
<td>516</td>
<td>31 (6%)</td>
<td>46 (8.9%)</td>
<td>4</td>
<td>76.8</td>
<td>v</td>
</tr>
<tr>
<td>Murthy et al., 2007 [16]</td>
<td>Israel</td>
<td>Retrospective</td>
<td>1065</td>
<td>172 (16.2%)</td>
<td>93 (8.7%)</td>
<td>32</td>
<td>54</td>
<td>v</td>
</tr>
<tr>
<td>Mousa et al., 2018 [147]</td>
<td>UK</td>
<td>Retrospective</td>
<td>227</td>
<td>25 (11%)</td>
<td>30 (13.2%)</td>
<td>–</td>
<td>37.4</td>
<td>×</td>
</tr>
</tbody>
</table>

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**Table VI**

**Association between infection and breast cancer recurrence**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Recurrence N (%)</th>
<th>Type of recurrence</th>
<th>Type of surgery</th>
<th>SSI definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdullah et al., 2019 [23]</td>
<td>107</td>
<td>8 (7.5%)</td>
<td>3 Local</td>
<td>Mastectomy + IBR</td>
<td>Infection</td>
</tr>
<tr>
<td>Beecher et al., 2016 [15]</td>
<td>229</td>
<td>49 (21.4%)</td>
<td>6 Local</td>
<td>Mastectomy + IBR</td>
<td>Would complication</td>
</tr>
<tr>
<td>Indelicato et al., 2007 [59]</td>
<td>516</td>
<td>31 (6%)</td>
<td>31 Local</td>
<td>Lumpectomy</td>
<td>Infection</td>
</tr>
<tr>
<td>Murthy et al., 2007 [16]</td>
<td>1065</td>
<td>172 (16.2%)</td>
<td>17 Local</td>
<td>Varied</td>
<td>Would complication</td>
</tr>
<tr>
<td>Mousa et al., 2018 [147]</td>
<td>227</td>
<td>25 (11%)</td>
<td>7 Local</td>
<td>Mastectomy + IBR</td>
<td>Infection</td>
</tr>
</tbody>
</table>

IBR, immediate breast reconstruction; SSI, surgical site infection.
Follow-up

Follow-up was considered as the length of time the patients were monitored for surgical complications, cancer recurrence or any adverse events after surgery. Seventy-four of the 99 papers from the SSI search recorded how long patients were followed for. The average follow-up was 17 months (±27.8 months), ranging from 2 weeks to 144 months. Nearly 30% of the studies (22) had a follow-up of one month. When comparing length of follow-up, the studies that followed the patients for one month or less had a mean SSI rate of 11%, while the studies that followed their patients for more than one month had a mean incidence of 13.4%. Although this increase is not large, it indicates that perhaps, if all the studies involved monitored their patients for an extended period of time, their incidence of SSI may have increased.

The mean follow-up period for the recurrence studies was 51 months, ranging from three to 144 months. Even though they had a longer follow-up period, they had a lower mean incidence of SSI of only 6.6%. This is due to the focus and design of the studies. Data were collected mostly on a retrospective basis (Table I), and SSI was not the primary outcome of the papers. Therefore, as a secondary outcome, there may have been inconsistencies in their recording.

Cancer recurrence

Breast cancer recurrence was mentioned in only 15 of the 99 papers in the SSI alone searches [22,23,32,45,59,61,64,70,78,79,82,93,95,104,105]; 8.6% of these patients developed recurrence after surgery. Incidences of recurrence and SSI were recorded independently of each other in the studies, rather than linked and correlated. This meant it was impossible to interpret the contribution SSI may have made to these recurrences. There was also no classification of the recurrences into their local or distant subtypes. This lack of clarity highlights the importance of the second search of this study for a more in-depth analysis of recurrence characteristics. Of the 17,569 patients in the recurrence-focused section of this review, there were 2077 cases where the breast cancer recurred (11.8%). The mean follow-up period was 51 months, ranging from three months to 144 months. There were 563 cases of LR, 1186 cases of DR, 25 recurred both locally and distantly, and 303 cases did not specify whether they were local or distant. The results are again limited by the fact that 16 of the studies only recorded LR, suggesting that perhaps there were more cases of DR that were not documented. This high rate of DR is especially worrisome as once the cancer has progressed to this stage, full recovery is unlikely.

Recurrence and SSI

Five studies (Tables V and VI) examined the association between SSI and later cancer recurrence [16,23,59,147,164]. They were all retrospective reviews of hospital patient charts and relatively small in size, with samples ranging from 107 to 1065 patients. They each recorded higher rates of infection (8.7%–17.8%) than the suggested 1–3% for clean surgeries. Four of the five papers stated whether or not the patients, whose cancer had recurred, had experienced an SSI at time of initial cancer surgery; 23.5% of the patients whose cancer had recurred had previously had an infection. Apart from Abdullah [23], Cox regression analysis was used to check for association between the initial SSI and subsequent hazard of developing a recurrence. Three of the studies found an increased likelihood of developing recurrence after acquiring an SSI [16,59,164] and two found no association [23,147]. The three papers that determined a positive association had longer postoperative follow-up times and larger sample sizes than those that found no association. Abdullah [23] only had one patient who experienced both recurrence and infection, and Mousa [147] did not state how many patients experienced both. These studies were limited by their small sample sizes and short follow-up periods. It cannot be ruled out that, if a longer follow-up time was employed and larger sample sizes, the studies would have exhibited the same association as the other three studies.

Other co-morbidities

The mean age of the breast cancer patients at time of surgery from the SSI and recurrence searches were very similar, 54.6 (±7.3) years and 53 (±8.1) years, respectively. The participants of this study had a mean BMI of 26.2 kg/m² (±2 kg/m²) and thus were considered overweight. There was a record of 52,221 patients smoking or having previously been a smoker before their primary breast cancer surgeries.

Discussion

This review addressed two principal areas: first, establishing the characteristics recorded regarding SSI after primary breast cancer surgery; and second, examining the events of breast cancer recurrence after SSI of the primary breast cancer surgical wound and the plausibility that they are linked.

The first aspect of this review extracted data from 484,605 patients in the 99 eligible studies (Figure 1) and the second, 17,569 patients from 53 studies. The results of this review suggest that the association between postoperative infection and adverse cancer outcomes is clear, but the cellular link between them remains elusive. There is evidence that specific bacterial species are associated with SSI from the breast surgical wound of the cancer patients. S. aureus, E. coli and P. aeruginosa were the most common causative bacterial species identified, consistent with emerging literature [165]. There was a high proportion of DRs. Five studies investigated the association between SSI and breast cancer recurrence with three concluding that an association did exist. Arising from this review, albeit that confounding factors make results challenging to compare and interpret, there are sufficient data to reasonably argue that a standardized prospective study with appropriate statistical power is warranted.

The SSI incidence rates reported in individual studies are quite variable, ranging from 0.2% to 48%. The majority of these were higher than the 1–3% suggested SSI rate for clean surgeries of the breast [9]. There are no obvious explanations for these inconsistencies in infection rates between institutions. Previously, it had been suggested that staff training, the experience of surgical and perioperative teams, and use of antimicrobials prophylactically may all contribute to these discrepancies [10,166]. Perhaps it proposes that the cancer itself may be playing a role in the development of these infections. This theory is supported by Olsen [11] who
examined both cancer and non-cancer patients undergoing breast surgery and found that the cancer patients had a higher incidence of SSI despite the fact that they have very similar surgical procedures in terms of duration and invasiveness. Interestingly, a recent study by Nejman [12] found that the bacterial load of the tumour microbiome was much larger than that of the normal breast samples, this was not the case for other cancers, such as lung and ovarian.

There was considerable variation in criteria used to define SSIs throughout the studies included in this review. Currently, there is no worldwide ‘gold standard’ classification method, making interpretation of the incidence rates challenging. Table IV demonstrates how four different definitions of SSI were used, but nearly 50% of studies did not mention whether they employed a specific definition. Notably, a study performed in the USA, found that by changing their definition of what constituted an SSI after breast surgery, by excluding cases of cellulitis, the incidence rate dropped from 8.7% to 2.7% [167]. Moreover, the retrospective nature of the majority of the studies may have influenced the SSI rate recorded, possibly resulting in higher rates due to follow-up being conducted on an outpatient basis. If an SSI developed but did not require readmission then it may not have been documented in the patient records, meaning it was not included in the study [16,76]. Almost one-third of the studies had a follow-up period of one month, owing to the fact that an SSI is typically defined as occurring within the 30-day time period after surgery [168]. However, in the latest guidelines published by the Centres for Disease Control and Prevention (CDC) they advise that a 90 day surveillance period for surgeries of the breast should be employed [169]. It is also worth noting that many of the papers did, in fact, monitor the patients postoperatively for much longer than the 30 day period suggested by the definition and, consequently, recorded a higher incidence of SSI than those only followed for one month. The mean rate of infection increased from 11%, for those monitored for 30 days, to 13.4% for those with a longer than 30 days follow-up period. However, it should be noted that more standardization across studies is needed in order to determine if this is a true difference. Other studies have found that it may be necessary to extend the surveillance to 265 days post-surgery in order to fully detect all SSIs [170–172]. Overall, this inconsistency in the numerous SSI definitions employed and capricious data-collection methods acts as a confounder of results, making it challenging to compare variables across studies.

The microbiome of breast tissue has normally been associated with Gram-positive phyla such as staphylococci species [173,174] but more recently it has been suggested that the epidemiology of the breast, especially breast tumours, is changing with more Gram-negative bacteria being identified in surgical wounds [165]. The results of this review support this, as it identified a much larger than expected volume of infections caused by Gram-negative bacilli, namely, E. coli and P. aeruginosa (Figure 2). This may be suggestive of poor hygiene and cleaning practices contaminating the surgical field or the wound itself. The method of obtaining cultures was not standardized; as such, some may have been obtained under sterile conditions, and others may have been superficial swabs. Methodological confounders may be reflected in studies whereby, for instance, all of the 43 reported cases of E. cloacae species were found by the Vilar-Compte group in Mexico [110–112]. Similarly, Rolsten et al. from the USA are unique in reporting Proteus mirabilis from the SSIs of the breast cancer patients in their institution in Texas [87,88]. This is suggestive of environmental factor or testing-related confounders that contribute to the outcomes of their studies.

There was a lack of detail regarding cancer recurrences in the papers included in the SSI portion of this review, possibly due to their shorter follow-up period. In the recurrence-focused section, there were 2077 cases of breast cancer recurrence (11.8%). Five-hundred and sixty-three of the cases were specified as LR, 1186 DR and 25 cases recurred in both local and distant sites. The remainder did not specify whether they were local or distant. Nearly half of the studies included in this review did not differentiate their results based on the different surgery types (Table III) making it difficult to compare results across studies and infer results. Relatively recently, it has been suggested that surgical trauma itself may influence the TME, encouraging the harbouring of dormant cancer cells, which may later circulate and initiate recurrence [175]. As well as this potential dissemination of tumour cells, surgery results in an increased immune response with increased release of growth factors that may stimulate residual cancer cells, influencing their behaviour and morphology, encouraging increased proliferation, invasion, migration and resulting in DR [176]. Augmenting our understanding of how these interact and influence this recurrence could prove vital in optimizing precision medicine to reduce the likelihood of recurrence-associated mortality.

The link between SSI and recurrence is underreported in the literature, with only five papers found to examine their association. Three of the studies found an increased likelihood of developing recurrence after acquiring an SSI [16,59,164] and two found no association [23,147]. Although it should be noted that the two studies that found no association employed shorter follow-up times and smaller sample sizes. This interrelation could be due to the fact that the immunogenic landscape of the breast wound after surgery is associated with inflammation, fever and release of cytokines and growth factors [177,178] and that breast cancer itself displays immunogenic properties [18]. If an infection were to be added on top of this, the TME may become further dysregulated. For example, endotoxin components of bacteria infecting wounds have been shown to activate the toll-like receptor pathway, triggering the intracellular signalling cascade to release pro-inflammatory cytokines [179]. SSIs also influence timing of adjunctive cancer therapies, such as radiotherapy and chemotherapy, delaying them by up to six weeks [180,181]. This increases the likelihood of cancer recurrence, as these therapies are essential to quickly eradicating the residual cancer cells after the tumour is removed, preventing their dissemination and regrowth. In breast cancer specifically, delay to radiotherapy has been associated with increased risk of recurrence and decreased overall survival [182,183]. In this review, Murthy [16] and Beecher [164] displayed very similar findings, both reporting that the probabilities of recurrence-free survival were reduced in patients who had developed an SSI versus those who had not. Indelicato [59] reported that each of their patients who failed local control
References


