Medical Hypotheses 144 (2020) 110057

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Proposed hypothesis and rationale for association between mastitis and breast cancer

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ABSTRACT

Breast cancer is amongst the most common forms of cancer, is predominantly a woman's illness, and is the most frequently reported invasive cancer in women worldwide (Bray et al., 2018). Varying risk factors have been identified, including genetics, family history, lifestyle, age and the use of hormone replacement therapy. Mastitis, also predominantly a woman's illness, is an inflammatory condition of the breast that, despite being an inflammation-related condition, is not currently considered a risk factor for breast cancer. This appears counterintuitive as epidemiological studies have identified chronic inflammation as a contributor to cancer risk, for example in gastric, oesophageal and colon cancers (Lin et al., 2016; Qadri et al., 2014; Principe et al., 2017). Previous reports have focused on women hospitalised for mastitis, and most commonly on puerperal mastitis, perhaps underestimating the relationship between breast cancer and non-lactational mastitis. Our hypothesis, based on systematic review, suggests that a longitudinal study of this disease, affecting women predominantly, is warranted.

Background to the hypothesis

Breast cancer is amongst the most common forms of cancer, is predominantly a woman's illness, and is the most frequently reported invasive cancer in women worldwide [1]. Varying risk factors have been identified, including genetics, family history, lifestyle, age and the use of hormone replacement therapy. Mastitis, also predominantly a woman's illness, is an inflammatory condition of the breast that can be caused by milk stasis or infection. It can also occur in non-lactational settings. However, despite mastitis being an inflammation-related condition, it is not currently considered a risk factor for breast cancer. This appears counterintuitive as epidemiological studies have identified chronic inflammation as a contributor to cancer risk, for example in gastric, oesophageal and colon cancers [2–4].

More specifically, the two main forms of mastitis are puerperal and non-puerperal, with the primary distinction related to whether or not mastitis occurs in a lactational setting. Puerperal mastitis, also referred to as lactation mastitis, is the more common, and is a result of milk stasis or infection occurring in women who have recently given birth and are, most likely, breast-feeding [5]. Milk stasis results typically from inefficient removal of milk from the breast causing breast inflammation and pain [6]. Unfortunately, milk stasis promotes development of an environment favourable to bacterial growth and infection. Additionally, in non-puerperal mastitis, also termed non-lactational mastitis, certain bacterial species may penetrate the breast causing infection. The bacterial species most associated with both forms of mastitis is coagulase positive *Staphylococcus aureus* [8], commonly found on the skin and in breast milk. Symptoms of mastitis are most often alleviated with removal of milk and/or the administration of antimicrobials [6]. Both forms of mastitis result in inflammation and both have the potential for manifest bacterial growth. A better understanding of the systemic effects on breast tissue is needed to elucidate any long-term effects resulting from the condition.

Given the known associations between inflammation and development of cancer, it appears rational to evaluate the potential relationship between mastitis-related inflammation and breast cancer, and it is surprising perhaps that this has not been done prior to this study. However, mitigating factors include a paucity of data published on the topic. We conducted a PRISMA-compliant systematic review using PubMed, Web of science, Cochrane and EMBASE databases (1990–2019). The following terms were used to identify articles: "mastitis" and "breast cancer" and "risk". Papers describing retrospective or prospective cohort studies that discussed incidence of breast cancer diagnosis in patients formerly diagnosed with mastitis were selected to determine the risk of breast cancer following development of mastitis. Additionally, appraisal included retrospective and prospective cohort studies of patients with a history of breast cancer and reporting subsequent diagnosis of mastitis.

The search yielded 318 unique articles. Notably, no studies were found that discussed mastitis rates in women with a history of breast

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https://doi.org/10.1016/j.mehy.2020.110057
Received 14 May 2020; Received in revised form 15 June 2020; Accepted 26 June 2020

cancer. Therefore, in-depth appraisal related to patients diagnosed with mastitis and diagnosed subsequently with breast cancer. It is worth noting that the amount of research focusing on this issue is meagre. However, four papers were identified that reported data relevant to the possibility of an association between mastitis and breast cancer [7–10]. All four studies referred to elevated incidence of breast cancer among women diagnosed with mastitis in comparison to women who had never been diagnosed with the disease.

In particular, Peters et al (Germany) [7] and Lambe et al (Sweden) [8] performed large population based studies, albeit that their focus was on different types of mastitis. Peters et al targeted non-lactational / nonpuerperal mastitis while the patient cohort in the Lambe et al study comprising puerperal mastitis patients predominantly (97%). Nonetheless, both studies detailed an increased incidence of breast cancer (1.8% and 1.23%, respectively). In particular, Peters and his colleagues [7] declared a "tentative" 37 fold increase in risk of cancer diagnosis within 12 months of treatment for women with nonpuerperal mastitis that had been diagnosed through clinical presentation, laboratory analysis or sonography. Although the increased risk was calculated using an age related standardised ratio the number of subjects diagnosed subsequently with breast cancer was relatively small, and the authors declared a bias. Specifically, in three of the five cases, non-palpable breast tumours were detected only by mammography. Indeed, the subjects of the Peters et al. study were screened for breast cancer twice within 12 months. The authors were open in saying that had they only done "one mammogram directly after healing" of the mastitis inflammation they would have missed those three cases [7].

Lambe et al. [8] performed an in-depth analysis of a larger cohort of Swedish women, reporting a modest increased risk of breast cancer incidence following mastitis. The study, however, was limited in its scope in that inclusion required hospitalisation (i.e., acute illness), and exclusion criteria involved: prior multiple births; prior diagnosis of mastitis or a diagnosis more than 12 months previously. The study, therefore, emphasised involvement of mastitis in a cohort of women that is narrower than the general population, and entertained only the possibility of mastitis involvement if occurrence was within one year of entry into the study. The reported incidence rate ratio was 1.23 (95% confidence interval = 1.02–1.49). Furthermore, confidence intervals pertaining to the laterality of mastitis and breast cancer ranged from 41% to 62%. Although a weak correlation exists, it is worth noting that data on laterality existed for only 87 of the total 106 women. While there are scientific and clinical rationales for the inclusion and exclusion criteria above, it seems reasonable to suggest that a more inclusive study population may have indicated greater association.

In contrast, the emphasis of the Ghadiri et al. study (Iran) [9] was quite narrow; specifically lactation discontinuation and affect on subsequent breast health. The reported data did not differentiate between breast abscesses and other benign diseases, no data were reported for mastitis patients independently, and hormone use (for HRT) was a confounder that was not appropriately dealt with. However, in short, the authors stated that those subjects who discontinued lactation following a diagnosis of mastitis had an increased rate of breast cancer compared with those who discontinued for other reasons. An increased rate of breast cancer was also reported in women who ceased lactation due to an intervening benign breast disease (odds ratio 3.669).

Most recently, in 2019 Chang et al. (Taiwan) [10] described a large study comparing incidence of breast cancer in women who experienced non-lactational mastitis as opposed to those who did not. Unlike the Peters et al. study [7], the comprehensive statistical approach used in Taiwan accounted for potential confounders such as socioeconomic demographics, hormonal medications and comorbidities that have known risk elevating association with breast cancer, such as hypertension, chronic obstructive pulmonary disease, thyroid disease, diabetes, hyperlipidemia and obesity. Crucially, four control women were matched to each woman with non-lactational mastitis. However, smoking and diet, family history and parity status were not considered, as such data were not accessible. Their outcome was a significant association between non-lactational mastitis and subsequent breast cancer. More precisely, compared with women in the comparison group, women who had non-lactational mastitis before the age of 40 years (aHR = 2.22, 95% CI: 1.18–4.18) and at the age of 40 to 49 years of age (aHR = 2.00, 95% CI: 1.11–4.04) had a significantly higher risk of breast cancer. However, women with lactational mastitis did not exhibit a statistically significant risk of developing breast cancer, relative to women in the comparison group. Furthermore, risk of breast cancer in women increased significantly as the number of non-lactational mastitis occurrences increased.

Statement of hypothesis

Our hypothesis, therefore, relates to the relationship between mastitis and breast cancer that has not been recognised broadly. Indeed, it is clear from the four significant studies described above that the association between mastitis, the more common puerperal form and the more infrequent non-lactational form, has been underestimated. The reasons for this relate largely to study inclusion criteria that have effectively narrowed relevance of the study outcomes to general populations, and interpretation of these outcomes to reduce the perceived risk of mastitis in the context of prior incidence of mastitis.

Mechanistically, the rationale for increased risk of breast cancer due to prior puerperal mastitis relates to bacterial infection and establishment of a promalignant environment. The role that bacteria play in development of cancers is now widely accepted [11]. There is increasing acceptance of the role of our microbiome in cancer development. The breast microbiome is distinctly diverse between benign and malignant diseases of the breast [12,13]. Indeed, there is evidence that a precancerous environment may actually be favourable to bacteria. For example, hypoxia is a common characteristic of oncogenesis and has been shown to increase cytotoxin production and biofilm formation of *Staphylococcus aureus* [14]. Furthermore, malignant cells maintain their intracellular pH level through an acid extrusion process [15] resulting in environmental acidification [16]. *S. aureus* achieves optimum growth between pH 6 and 7, provided for in breast malignancy with associated environmental pH ranges of between 6.5 and 6.7 [16].

The consequence of mastitis-related bacterial proliferation is inflammation, recognised as an initiator for cancer [17,18]. There are two primary outcomes relevant to cancer development.

Firstly, recruitment of phagocytes to an area of infection results in the secretion of proinflammatory cytokines and adipokines. These, in turn, attract more immune system cells and elevate the inflammatory response. This mediates intracellular signalling, which can induce pathways that activate oncogenic mutations and transcription of proteins involved in the initiation and promotion of cancers [18]. Some cytokines and adipokines controversially associated with breast cancer include leptin, interlukin-6 (IL6), adiponectin and Tumour Necrosis Factor-α (TNF-α). The latter association is debated consistently due to contradicting literature. However, the ability of TNF-α to activate NF-κB, promoting cell cycle and cell proliferation and its ability to stimulate estrogen synthesis contributes to its cancer promoting reputation [18]. More certain is IL6 as an activator of the Janus kinase pathway. This pathway is involved in initiating the transcription of a well known oncogene MYC and other inflammatory cytokines such as IL8. This promotes a reciprocal feedback loop to manipulate an environment favourable to oncogenesis [18].

Separately, the rationale for increased risk of breast cancer due to prior non-puerperal, non-lactational mastitis relates to damage of the extracellular matrix (ECM) of the breast (caused potentially by mastitis at a young age) and could be a significant contributor to breast cancer development. A multifaceted network of proteins and glycoproteins that is required to maintain tissue homeostasis, the ECM is crucial in regulating cellular behaviour [19]. Mastitis and associated inflammation during a time of development could result in dysregulation that

leaves a woman more susceptible to breast cancer [20]. Mastitis-associated immune cascade may promote hormonal imbalances and greater risk of breast cancer [21].

Testing the hypothesis

Certainly, this hypothesis is limited by the availability of literature on this subject. However, the large population based cohorts described here strengthen the argument that mastitis could reasonably be proposed to increase the risk of breast cancer. Crucially, mastitis is a possible risk that can potentially be mitigated in contrast to other breast cancer risk factors, for example, family history and aging. The most common form of the disorder, puerperal mastitis, occurs at a time when women are in regular contact with medical practitioners and the use of preventative measures (e.g., ensuring sufficient milk flow) could reduce a woman's likelihood of developing mastitis. It seems evident that large-scale, prospective longitudinal studies are warranted investigating puerperal and non-puerperal mastitis. Prospective studies focused on both forms of the disease may discern any mechanistic differences between them, and the effect these may have on breast cancer risk. Such studies should involve broad age groups, take into consideration potential confounders including lifestyle factors (e.g., diet, smoking, alcohol & substance abuse, socioeconomic demographics, history of childbirth, comorbidities, medicines intake, etc), surveillance and screening of women immediately following diagnosis of mastitis and continuing with multiple mammograms for at least 12 months following alleviation of symptoms or resolution of mastitis; and (where feasible and ethically appropriate) collection of biopsy specimens for correlation of biomarkers at time of surgery, if required.

Such a suitably-powered and resourced investigation would present an opportunity to more clearly understand this aspect of women's health and reduce risk of this potentially lethal disease.

Funding

There was no funding for this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110057.

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