Breast Cancer and Psychological Stress: Experimental Models

Deborah A. Cory-Slechta
Departments of Environmental Medicine and Pediatrics
University of Rochester School of Medicine, Rochester NY

INTRODUCTION

Animal Models of Stress:

Experimental studies of stress predominantly rely on rat and mouse models, although occasionally primate studies have been done. Multiple different experimental models of stress have been utilized and it has become quite clear that different types of stress can produce markedly different biochemical, physiological and behavioral consequences (Bowers, Bilbo, Dhabhar, & Nelson, 2008; Dayas, Buller, Crane, Xu, & Day, 2001; Gavrilovic & Dronjak, 2005; Lenox et al., 1980; Pajovic et al., 2006). Further, some of these stressors are only relevant in a sex-dependent context, for example intruder stress is widely used for male rodents, but is not particularly relevant in the case of females. Thus, it is somewhat simplistic to generalize effects of a study across stressors, but of course it is widely done, nevertheless. Additionally, stress is often described in experimental studies as being either acute or chronic, with little definition of what constitutes chronic. In some cases, a stressor is imposed as a baseline to determine later response to a stress challenge as well, producing a type of 'cumulative' stress model. Another approach for chronic models is to impose a different stressor stimulus each day over the period of stress such that the paradigm is described as chronic variable stress or chronic variable unpredictable stress.

Probably the most widely and thus best physiologically characterized is restraint stress. In one model of restraint stress, a rodent is placed in a cylinder in which it cannot move, turn around, etc. (described as the ecological equivalent of having a rat burrow collapse, although this in the wild would still offer an escape potential for a rodent). The other most widely used method of restraint stress is to place the rodent in a supine position on a board and to tape down all of its extremities to prevent any movement or escape. In addition to restraint stress, other methods have included placement in a cold room for some period of time, introduction of an intruder into the animal's home cage, the use of loud noise/lights, introduction of the smell of predator urine, and forced swimming for some duration in a pool of water from which escape is not possible.

It has been argued that restraint stress is a non-ecologically relevant model for human stress in breast cancer studies (e.g., (Trainor, Sweeney, & Cardiff, 2009) and it would be possible to make similar statements about many of these stress paradigms, as directly modeling human stress in animal models can be difficult.

Most of the more recent experimental studies of breast cancer and stress to date have adopted another stress paradigm, which has also been in use for a prolonged period although it is less well characterized than restraint, which is the use of isolation vs. group housing (social isolation). Both rodents and primates are social species and thus live in group situations, which clearly makes the stressor somewhat more relevant. Social isolation is considered to be an analogue of deprivation of a social support structure that has been shown to be critical to stress mitigation in humans, although this may be a somewhat anthropomorphic interpretation. Nevertheless, social isolation is a widely used stress paradigm, although there have been some inconsistencies in the biochemical and physiological changes with which it has been associated, and which can therefore impact interpretations in some of the breast cancer and stress studies.

Stress is both Detrimental and Beneficial:

It is critical to appreciate that stress is by no means a unitary concept, but actually a construct. Stress can have both beneficial effects as well as long-term adverse consequences. More specifically, it has been known for some time, and recommended that the term stress be restricted to an independent variable determined to be an aversive stimulus that is both uncontrollable and unpredictable from the organism's point of view. In contrast, stressor stimuli that are predictable and controllable should not be deemed as 'stressors' per se and are thought to be the path to the

induction of resilience. The best studies demonstrating the associated differences have come from Maier's group (e.g., (Kubala, Christianson, Kaufman, Watkins, & Maier, 2012; Rozeske et al., 2011; Varela, Wang, Christianson, Maier, & Cooper, 2012) in which tail shocks are delivered to rats; for one group, a response can terminate the tail shock, while a yoked group receives exactly the same tail shock schedule, but cannot effect any response to terminate these. Despite the fact that both groups receive identical numbers and levels of shock, biochemical differences and subsequent behavioral consequences between them can be pronounced. Rats that can terminate (control) the shock are considered to develop a 'resilient' phenotype, whereas those that experience uncontrollable and unpredictable shock suffer the adverse consequences. Strikingly, this understanding has yet to be systematically incorporated into experimental stress studies, so that: 1) in most cases, comparisons of uncontrollable/unpredictable stress to controllable/predictable stressors are not included; and 2) whatever stressor/stress paradigm that is used is assumed to be adverse and thus detrimental. Consequently, in interpretation of breast cancer and stress studies, it is critical to evaluate the extent to which the stressor would have been, or remained as chronic, uncontrollable/unpredictable from the animal's point of view, or whether it eventually became predictable/controllable. The stress parameters may directly influence whether either facilitory effects or inhibitory effects on cancer are seen.

Stress Effects are Highly Gender Dependent:

It is also quite clear from the experimental stress literature that stress effects are highly gender dependent in their consequences (Dalla, Pitychoutis, Kokras, & Papadopoulou-Daifoti, 2011; Huang, Chen, Yeh, & Hsu, 2012; Simpson & Kelly, 2012; Sterrenburg et al., 2011; Trainor, 2011). Consequently, the results of studies carried out in male animals may not necessarily generalize to females, where breast cancer is of far greater prevalence.

Timing of Stress Effects is an Important Variable:

The time in development or life span at which the stressor is applied is of particular interest in studies of breast cancer and stress for at least two reasons. First, some studies have examined stressor exposures early in development, which may have a different pattern of effect on sex hormones than those applied during adulthood or later. Additionally, timing of stressor in relation to the period of mammary gland development may also be critical in terms of potential changes in mammary morphology and function and associated estrogen function since many breast tumors are estrogen dependent.

BIOLOGICAL BASES FOR STUDYING STRESS AS A CONTRIBUTOR TO BREAST CANCER

Stress is considered to be a potential contributor to the initiation and to the progression of cancer. In any studies of interactions of variables such as stress and breast cancer, it is critical that the risk factors share some biological substrates to provide a biological basis for interactions. In that regard, there are multiple mechanisms by which stressors can impact, both directly and indirectly, known mechanisms of breast cancer onset and or progression. One such important mechanism related to tumor progression is glucocorticoid signaling which can inhibit cancer cell death pathways and promote cancer cell survival in the face of chemotherapy (Volden & Conzen, 2013). Stress exposures early in life can permanently alter the hypothalamic-pituitary-adrenal (HPA) axis which influences mammogenic reproductive hormones through interactions with both the limbic-hypotalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gondal axis. Such disruptions can lead to abnormal sex hormone levels (e.g., estrogen) and to altered mammary gland development. Thus, it is clear that interactive biological pathways support the potential for interactions of psychosocial stress with breast cancer pathway (Armaiz-Pena, Lutgendorf, Cole, & Sood, 2009; Trainor et al., 2009).

One additional caveat in interpretation of the experimental studies is the recognition that glucocorticoid receptor (GR) functions are well known to be non-linear (e.g., (Du et al., 2009) such that both a hyperresponsive HPA axis and a hyporesponsive HPA axis are damaging.

STUDIES OF BREAST CANCER AND STRESS IN ANIMAL MODELS

Studies: Studies of breast cancer and stress were frequently differentiated on the basis of whether they examined initiation, progression, and even to resistance to chemotherapy. Obviously some studies were stronger than others, as based not only on experimental design, but also on factors related to stress as described above. While there is a relatively extensive literature overall on stress and cancer, there are surprisingly fewer studies specifically devoted to stress and breast cancer. These first appeared between the 1980s-2000s during a period that reflected a broad interest in stress and cancer (Sklar & Anisman, 1980, 1981). This was followed by a lull in breast cancer and stress studies, after which studies began to appear again between 2008-2013 suggesting a renewed interest.

Studies of breast cancer and stress have used a range of stressors, as well as different methods of inducing breast cancer. This could actually be useful in that it permits an assessment of the generality of the stress effects across different breast cancer models. In general, the more recent studies are stronger and of more direct relevance to the human environment, as will be summarized below.

Early studies focused on the use of 1,12-dimethylbenz-(a)-anthracene (DMBA) to induce mammary tumors in female rats and used a range of very intense stressors that were applied in a protracted fashion. These included foot shocks (Newberry, Frankie, Beatty, Maloney, & Gilchrist, 1972; Pradhan & Ray, 1974; Ray & Pradhan, 1974), electroconvulsive shock (Pradhan & Ray, 1974), electroconvulsive shock and/or sound (Bhattacharyya & Pradhan, 1979; Pradhan & Ray, 1974) or restraint stress (Bhattacharyya & Pradhan, 1979; Newberry, 1978; Newberry, Gildow, Wogan, & Reese, 1976). Counter to expectations, virtually all of these studies reported an inhibition of the growth of DMBA-related mammary tumors. In some cases this included either decreases in numbers of tumors or in the size of these tumors. In some of the studies, these effects were accompanied by reductions in body weight of stressed rats, and or decreases in organ weights such as adrenal weights or uterine or ovary weights, suggesting additional physiological deficits. While the timing of the stressors differed, and in some cases was directly investigated in the study, these were often quite protracted in duration. In the studies of the Pradhan group (Bhattacharyya & Pradhan, 1979; Pradhan & Ray, 1974; Ray & Pradhan, 1974), for example, stressor stimuli were applied daily for periods that included 6 days per week (Ray and Pradhan, 1974) for up to at least 30 days (methodological details are not sufficient to gauge the exact dates). Pradhan and Ray (Pradhan & Ray, 1974) administered shocks 6 days/week for 4-7 weeks. Shock levels used in these studies were also extraordinarily high. Newberry et al. (Newberry et al., 1972) administered shock stress to rats for up to 85 consecutive days. Forced restraint was used in Newberry et al. (Newberry et al., 1976) for periods of 5 or 10 hrs per day from 35 to 108 days of age. In another study Newberry imposed restraint stress for 12 or 14 hrs/day for periods of approximately 20 days (Newberry, 1978).

These experiments are difficult to interpret for several reasons. First, the extended duration of the stressor applications would suggest that these stressors could become highly predictable to the organism and controllable in the sense that the organism would learn that they were of finite duration with each application. As such, these stimuli could have transitioned to stressors more associated with resilience than with damage. If so, they might be more consistent with an inhibitory effect on mammary tumors as was indeed seen. The physically extreme nature of the stressors raises the question as to their potential to induce other physiologic changes that influenced outcome. Indeed, in some of these studies, decreases in organ or body weights were seen, although this information was not consistently provided.

The relevance of these particular experiments is also questionable. The extreme magnitude of the stressors for such a protracted period would not seem to be a model necessarily consistent with human stress. Indeed, this point was raised in the studies that were reported between 2008-2013. Moreover, the nature of these particular stressors, as addressed above, may be of less relevance to human stress than later studies that used isolated (social isolation) vs. group housing. Additionally, in virtually all of these studies, animals were individually housed, which is itself a known stressor (Ros-Simo & Valverde, 2012; Weintraub, Singaravelu, & Bhatnagar, 2010) and

therefore stressor stimuli applied experimentally were superimposed upon a physiological state already altered as a consequence of individual housing of the rodents.

A study by Weisenberg and Emerman (Weinberg & Emerman, 1989) utilized a different strategy to address the question of the role of stress in breast cancer. This study used a stress paradigm of perhaps more direct relevance to the human environment. Specifically, this group showed that mice housed individually over the entire experimental period or initially housed in a social group and then moved to individualized housing had markedly increased tumor growth relative to mice that were reared in groups over the entire experimental duration. In a subsequent study by this group (Grimm, Emerman, & Weinberg, 1996) using the same stressors and mammary cancer-inducing parameters, the effect was replicated and it was additionally demonstrated that dominance status interacted with housing condition, such that dominant mice moved from individualized to group housing demonstrated faster tumor growth, whereas dominant males housed in groups throughout the experiment had slower tumor growth rates. Aggressive behavior was thus suggested to modulate differential tumor growth. The interesting aspect of these papers was that in this experiment, stress enhanced, not inhibited tumor growth. While intriguing, the major limitation of these particular studies was that male mice were used with an SC115 tumor subline that is androgen-dependent, raising questions about its generality to human breast cancer.

A subsequent study of this group used a modified approach (Kerr, Wilkinson, Emerman, & Weinberg, 1999) in which a variant (SC115V) of the SC115 androgen dependent inducer was administered to both males and females. SCII5V is androgen independent. In addition to examining the impact of housing conditions as described above, half of the animals in each group were also subjected to an acute stress consisting of exposure to a novel environment, a strategy that provides a more 'cumulative' stress approach. In the case of males, the non-androgen dependent mammary tumor growth rates did not differ by housing condition per se, but acute daily novelty stress increased tumor growth in males moved from group to individualized housing relative to those moved from individualized to group housing. In females, tumor growth rate was enhanced when mice were moved from group to individualized housing as compared to females moved from individualized to group housing, essentially confirming what was previously observed in males with the androgen-dependent tumor line. Surprisingly, acute daily novelty stress actually significantly decreased tumor growth in females moved from group to individualized housing, as compared to those moved from individualized to group housing. The authors posit that the fact that females exhibit greater adaptivity to stress and or differential HPA axes effects may at least in part underlie this counter-intuitive result, but it is difficult to interpret these latter outcomes.

In the only study to date in non-human primates, social subordination increased mammary gland cell proliferation and thickness (Shively, Register, Grant, Johnson, & Cline, 2004), an effect that did not seem to be further enhanced by alcohol.

A somewhat complex study during this period (Hilakivi-Clarke, Wright, & Lippman, 1993) examined the impact of handling of rat pups from postnatal days 5-20 on the growth of DMBA-induced tumors in female Sprague Dawley rats. Pups were either held in a hand, or were administered an i.p. saline injection. These animals were also subjected to a forced swim (from which escape is not possible) stressor. Females that were injected daily, but not those that experienced handling alone, were protected, i.e., demonstrated longer survival and lower mammary tumor incidence. Although the authors posit a mechanism related to body weight for these findings, they are more suggestive of a type of stress resilience arising from the daily saline injection which is of course far more invasive than simple handling. Moreover, given that it occurred daily for 15 days, this stressor became both predictable (finite in duration) and controllable.

A couple of studies during this period focused on metastatic aspects of breast cancer and its interaction with stress. One (Ben-Eliyahu, Yirmiya, Liebeskind, Taylor, & Gale, 1991) demonstrated a twofold increase in the metastatic capacity of a syngenic mammary tumor (MADB106) in response to an acute intense stress (inescapable drowning) in male Fischer 344 rats. Again, given that this was carried out in male rats, and used a very intense stress, its direct relevance is questionable to the predominance of breast cancer in females in the human environment. In contrast, female mice that experienced daily injection of drugs for up to 700 days showed an

increase in number of and percentage area (size) of metastases of MTV-induced breast cancers to pulmonary hilus (Freire-Garabal et al., 2004). In the absence of documentation of HPA axis changes such as cortisol, and given the extended period of time over which injections were imposed, it would seem that this stressor may have transitioned from an unpredictable, uncontrollable stressor to one with predictive and controllable features, and act in a protective capacity. Yet this stress paradigm was shown in a prior study by these authors to increase mammary tumor incidence and decrease latent periods to onset of the development of MTV-induced mammary tumors in female mice (Freire-Garabal, Nunez, Balboa, Suarez, & Belmonte, 1992). While the overall findings concur with the report by Ben- Eliyahu (Ben-Eliyahu et al., 1991), it is difficult to see how this stressor would not have reverted to one that was more controllable and predictable from the organism's point of view, but yet it was associated, even the placebo injection, with enhanced breast cancer metastases. Such findings underscore the need to determine the extent of stressor vs. resilience-inducing properties of these stimuli.

With respect to the interaction of stress with the efficacy of chemotherapeutic treatment for breast cancer, very little research has been reported. Interestingly, restraint stress can enhance resistance to chemotherapy (Su et al., 2005), with restraint stress inhibiting tumor regression under chemotherapy in SCID mice.

After what appears to be a lull in interest in breast cancer and stress, a group of studies emerged in the last 5 years. Most prominent among these are several from the Conzen and McClintock laboratories. These studies have all generally utilized social isolation as a stressor in female Sprague-Dawley rats, a strain highly prone to development of spontaneous mammary tumors. Thus, the studies have a high degree of relevance to human breast cancer. In addition, they include numerous ancillary measures that permit assessment of the HPA axis response as well as more molecular markers related to mammary tumors.

A first such study (Yee, Cavigelli, Delgado, & McClintock, 2008), which was actually an assessment of social relationship status and breast cancer, defined individual subjects as being of neophobic or neophilic temperament, using behavioral tests in triads of female littermates. These females were exposed to a novel environment at 20 days of age, to cage relocation in adulthood, and to restraint stress in old age. Affiliative reciprocity (behavioral interactions among organisms) was measured during the home cage relocation stressor; corticosterone measured in response to restraint stress. Results showed that rats that did not interact reciprocally (low sociality) showed a shorter latency to palpable mammary tumors, these rats likewise displayed an enhanced corticosterone response to restraint stress. The findings were consistent with a protective or buffering effect of social interactions in reducing breast cancers, and/or with increased social isolation as enhancing breast cancer progression.

Hermes and McClintock (Hermes & McClintock, 2008) also examined the impact of prolonged social isolation (group vs. individualized housing) imposed early in life on ovarian function in young adulthood and middle age and mammary gland development at puberty, as well as mammary tumor burden in middle age in female Sprague Dawley rats. Evaluated at puberty, social isolation was found to delay development of mammary gland and to concurrently accelerate maturation of ovarian function, which, together, would prolong exposure of breast tissue to higher levels of estrogen. By midlife, social isolation stress had increased tumor burden, even though isolation had also led to premature estropause. Thus an estrogen-independent stress-induced enhancement of mammary tumors was seen.

These findings were again confirmed in a subsequent study (Hermes et al., 2009) which demonstrated an 84 fold increase in tumor burden in social isolates, with a 3.3 fold increase in risk for ductal carcinoma in situ and invasive ductal carcinoma. This was accompanied by a permanent alteration in HPA axis response that included enhanced response to acute stressors and delayed recovery (glucocorticoid negative feedback), suggesting an important role for glucocorticoid signaling abnormalities in mammary tumors (Volden & Conzen, 2013). An extension of these studies to female C3(1)/SV40 T-antigen mice (a transgenic model of triple negative mammary cancer) confirmed the findings previously seen in rats, showing that socially isolated females exhibited a larger mammary gland tumor burden and expression of genes of lipid synthesis and

glycolytic pathways known to contribute to increased breast cancer growth, than did group housed transgenic females (Williams et al., 2009). Additionally, socially isolated transgenic females exhibited an enhanced corticosterone stress response, again consistent with the involvement of glucocorticoid signaling in tumor growth. The increase in expression of metabolic gene expression in socially isolated mice in these studies was associated with the adipocyte rather than epithelial fraction of the epithelial cells and increased glucose metabolism, lipid synthesis and leptin secretion from the adipose depot, findings consistent with the hypothesis that social isolation results in metabolic reprogramming in mammary gland adipocytes that increases proliferation of adjacent preinvasive malignant epithelial cells (Volden et al., 2013).

In concert with the studies of the Conzen and McClintock group above, mice exposed to a severe (4 hrs day) maternal separation from postnatal days 2-22, but not those separated for only 15 min/day, were found to have a higher incidence and more rapid onset of mammary tumorigenesis following DMBA administration in adulthood (Boyd et al., 2010). This was accompanied by upregulation of estrogen receptor α in mammary gland. Thus, this study supports the work from the Conzen and McClintock group, using another model of early social stress. Similarly, adult female severe combined immunodeficiency mice that were moved from grouped into isolated housing after the development of palpable tumors in response to administration of the breast cancer cell line MDA-MB231 (a β-adrenergic receptor expressing line), showed a transient increase in tumor growth as well as increased weight and reduced norepinephrine concentrations in spleen (Madden, Szpunar, & Brown, 2013). In addition, social isolation increased levels of CD11b+Gr-1+, CD11b+Gr-1- and F4/80+ macrophage populations, consistent with a macrophage-mediated effect on mammary tumors. Interestingly, the enhanced tumor growth was transient, as were changes in peripheral norepinephrine concentrations, consistent with the possibility of behavioral adaptation/homeostasis, as might be expected with prolonged stress where conditions become more predictable and controllable to the organism.

Only one study (Hasen, O'Leary, Auger, & Schuler, 2010) has reported an effect that is inconsistent with the story above. In that study, wild type and $p53^{+/-}$ female mice housed individually from weaning exhibited significantly delayed mammary development relative to group housed controls; but individual housing did not increase mammary tumorigenesis. Instead, $p53^{+/-}$ group housed females exhibited significantly higher numbers of mammary tumors than did individually housed females. The reason for this contradictory finding is unclear. The p53 heterozygote was developed in the FVB mouse strain, the same strain used by Williams et al (Williams et al., 2009) in extending the findings of the Conzen and McClintock laboratories from the female Sprague Dawley rat model. As of yet, these protective effects of individualized housing and the higher incidence of mammary tumors in $p53^{+/-}$ group housed females does not appear to have been replicated either by the authors or by other investigators.

Summary:

In summary, despite a relatively large literature on cancer and stress more generally, the number of studies examining the effects of stress and breast cancer has been surprisingly small. In essence, these studies seemed to have occupied two time frames, with a first such group of studies published primarily between the 1980's-2000. The earliest studies found protective effects of stress against breast cancer, but these studies are difficult to evaluate. They used excessively high levels of stress, raising the possibility of numerous physiological consequences, which included in some studies decreases in both organ and body weights; functional physiological parameters were mostly not measured. Moreover, they employed stressors that may have the least validity with respect to human stressors.

Subsequent efforts have all generally relied on individual housing (social isolation) as a stressor, an approach first employed by the Weinberg laboratory (Weinberg & Emerman, 1989). The later studies have differed in breast cancer induction parameters, species, stressor timing etc. In contrast to the earlier group of studies, the majority of these later studies are consistent with the assertion that stress increases the progression, growth and even resistance to chemotherapeutic treatment of breast cancer. The studies by the Conzen and McClintock laboratories constitute the

strongest of these studies in terms of relevance to the human environment, experimental design and the assessment of the generality of the findings across species, assessment at multiple time points, as well as involvement of genetic variants.

RESEARCH GAPS

Despite the fact that studies of breast cancer and stress first appeared back in the 1970s and 1980s, the number of studies is relatively limited. It can generally be held, on the basis of published reports, that the understanding of this interaction remains in its infancy. Even if one accepts the conclusions from the later and stronger studies described above that appeared between 2008-2013, which, with one exception, find an enhancement of breast cancer parameters in relation to a stressor considered to be an analogue of social structure deprivation, there is still very limited knowledge. In fact, far greater characterization of the current models, allowing more refined focus in subsequent studies, is a critical need. First, most of these more recent studies have come from a single laboratory. Even though they have found a positive association in both rat and mouse studies, the generality of the effects is not clear since the same stressor model has been used in both cases. Thus it would be important to see confirmatory findings from other laboratories. Moreover, the extent to which other stressors reproduce these findings would be important to understand. In addition, at the current time, it is not clear to what extent enhancement of breast cancer effects by stress relates to the type of cancer induction model and to the estrogenic dependency (or not) of that model.

It cannot be ascertained at the current time how effects reported so far relate separately to initiation and/or progression of cancer. In addition, timing of the stressor needs to be varied so that particular periods of vulnerability may be determined. For these reasons, studies that include multiple time points of assessment are required.

FUTURE DIRECTIONS

First and foremost for future studies of the impact of stress on breast cancer is a need for systematic comparisons of the effects of uncontrollable/unpredictable stressors and controllable/predictable stressors, as one could hypothesize that the former should result in enhancement of breast cancers, while the latter, by promoting resilience, would be hypothesized to attenuate such effects. Since there are different types of breast cancers, and estrogen-sensitive breast cancers predominate, it would seem more logical to begin the process by using breast cancer models such as DMBA or genetic variants that permit estrogen receptor modification. Additionally, such studies could then incorporate tamoxifen treatments in terms of therapeutic mitigation.

It would also appear that comparisons of stressor timing will be critical to understanding the relationship of stress to breast cancer. A few studies have suggested the importance of fetal stress with consequent changes in mammary development as setting the stage for subsequent breast cancer. In studies imposing stress later in the life span, some inconsistencies are apparent in terms of exposures to stress prior to vs. after the administration of the breast cancer inducer. Consequently, studies systematically comparing the timing of stress (e.g., early in development during development of the mammary glands and ovaries, in adolescence prior to administration of breast cancer inducers, post administration of stress cancer inducers, and during old age after such induction) would be useful.

Given that human stress is generally more ‘cumulative’ in nature, subsequent studies could begin to look at more cumulative stress, i.e., intermittent stress models. Incorporation of stress models other than individual housing (social isolation) also need to be included. For example, to achieve uncontrollable and unpredictable stress, some experimental approaches have included the imposition of a different stressor at each stress point over some period of time

REFERENCES

Armaiz-Pena, G. N., Lutgendorf, S. K., Cole, S. W., & Sood, A. K. (2009). Neuroendocrine modulation of cancer progression. [Research Support, N.I.H., Extramural

Review]. *Brain, Behavior, and Immunity, 23*(1), 10-15. doi: 10.1016/j.bbi.2008.06.007

Ben-Eliyahu, S., Yirmiya, R., Liebeskind, J. C., Taylor, A. N., & Gale, R. P. (1991). Stress increases metastatic spread of a mammary tumor in rats: evidence for mediation by the immune system. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, Non-P.H.S.

Research Support, U.S. Gov't, P.H.S.]. *Brain, Behavior, and Immunity, 5*(2), 193-205.

Bhattacharyya, A. K., & Pradhan, S. N. (1979). Effects of stress on DMBA-induced tumor growth, plasma corticosterone and brain biogenic amines in rats. [Research Support, U.S. Gov't, P.H.S.]. *Research Communications in Chemical Pathology and Pharmacology, 23*(1), 107-116.

Bowers, S. L., Bilbo, S. D., Dhabhar, F. S., & Nelson, R. J. (2008). Stressor-specific alterations in corticosterone and immune responses in mice. [Research Support, N.I.H., Extramural

Research Support, U.S. Gov't, Non-P.H.S.]. *Brain, Behavior, and Immunity, 22*(1), 105-113. doi: 10.1016/j.bbi.2007.07.012

Boyd, A. L., Salleh, A., Humber, B., Yee, J., Tomes, L., & Kerr, L. R. (2010). Neonatal experiences differentially influence mammary gland morphology, estrogen receptor {alpha} protein levels, and carcinogenesis in BALB/c mice. [Research Support, Non-U.S. Gov't]. *Cancer Prev Res (Phila), 3*(11), 1398-1408. doi: 10.1158/1940-6207.CAPR-10-0111

Dalla, C., Pitychoutis, P. M., Kokras, N., & Papadopoulou-Daifoti, Z. (2011). Sex differences in response to stress and expression of depressive-like behaviours in the rat. [Research Support, Non-U.S. Gov't

Review]. *Curr Top Behav Neurosci, 8*, 97-118. doi: 10.1007/7854_2010_94

Dayas, C. V., Buller, K. M., Crane, J. W., Xu, Y., & Day, T. A. (2001). Stressor categorization: acute physical and psychological stressors elicit distinctive recruitment patterns in the amygdala and in medullary noradrenergic cell groups. [Research Support, Non-U.S. Gov't]. *European Journal of Neuroscience, 14*(7), 1143-1152.

Du, J., Wang, Y., Hunter, R., Wei, Y., Blumenthal, R., Falke, C., . . . Manji, H. K. (2009). Dynamic regulation of mitochondrial function by glucocorticoids. [Research Support, N.I.H., Extramural

Research Support, N.I.H., Intramural

Research Support, Non-U.S. Gov't]. *Proceedings of the National Academy of Sciences of the United States of America, 106*(9), 3543-3548. doi: 10.1073/pnas.0812671106

Freire-Garabal, M., Nunez, M. J., Balboa, J. L., Suarez, J. A., & Belmonte, A. (1992). Effects of alprazolam on the development of MTV-induced mammary tumors in female mice under stress. *Cancer Letters, 62*(3), 185-189.

Freire-Garabal, M., Rey-Mendez, M., Garcia-Vallejo, L. A., Balboa, J., Suarez, J. M., Rodrigo, E., . . . Nunez, M. J. (2004). Effects of nefazodone on the development of experimentally induced tumors in stressed rodents. *Psychopharmacology, 176*(3-4), 233-238. doi: 10.1007/s00213-004-1909-4

Gavrilovic, L., & Dronjak, S. (2005). Activation of rat pituitary-adrenocortical and sympatho-adrenomedullary system in response to different stressors. [Research Support, Non-U.S. Gov't]. *Neuro Endocrinol Lett, 26*(5), 515-520.

Grimm, M. S., Emerman, J. T., & Weinberg, J. (1996). Effects of social housing condition and behavior on growth of the Shionogi mouse mammary carcinoma. [Research Support, Non-U.S. Gov't]. *Physiology and Behavior, 59*(4-5), 633-642.

Hasen, N. S., O'Leary, K. A., Auger, A. P., & Schuler, L. A. (2010). Social isolation reduces mammary development, tumor incidence, and expression of epigenetic regulators in wild-type and p53-heterozygotic mice. [Research Support, N.I.H., Extramural

Research Support, U.S. Gov't, Non-P.H.S.]. *Cancer Prev Res (Phila), 3*(5), 620-629. doi: 10.1158/1940-6207.CAPR-09-0225

Hermes, G. L., Delgado, B., Tretiakova, M., Cavigelli, S. A., Krausz, T., Conzen, S. D., & McClintock, M. K. (2009). Social isolation dysregulates endocrine and behavioral stress while increasing malignant burden of spontaneous mammary tumors. [Research Support, N.I.H., Extramural
Research Support, U.S. Gov't, Non-P.H.S.]. *Proceedings of the National Academy of Sciences of the United States of America, 106*(52), 22393-22398. doi: 10.1073/pnas.0910753106
Hermes, G. L., & McClintock, M. K. (2008). Isolation and the timing of mammary gland development, gonadarche, and ovarian senescence: implications for mammary tumor burden. [Research Support, N.I.H., Extramural
Research Support, U.S. Gov't, Non-P.H.S.]. *Developmental Psychobiology, 50*(4), 353-360. doi: 10.1002/dev.20295
Hilakivi-Clarke, L., Wright, A., & Lippman, M. E. (1993). DMBA-induced mammary tumor growth in rats exhibiting increased or decreased ability to cope with stress due to early postnatal handling or antidepressant treatment. *Physiology and Behavior, 54*(2), 229-236.
Huang, C. C., Chen, J. P., Yeh, C. M., & Hsu, K. S. (2012). Sex difference in stress-induced enhancement of hippocampal CA1 long-term depression during puberty. [In Vitro
Research Support, Non-U.S. Gov't]. *Hippocampus, 22*(7), 1622-1634. doi: 10.1002/hipo.21003
Kerr, L. R., Wilkinson, D. A., Emerman, J. T., & Weinberg, J. (1999). Interactive effects of psychosocial stressors and gender on mouse mammary tumor growth. [Comparative Study
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.]. *Physiology and Behavior, 66*(2), 277-284.
Kubala, K. H., Christianson, J. P., Kaufman, R. D., Watkins, L. R., & Maier, S. F. (2012). Short- and long-term consequences of stressor controllability in adolescent rats. [Research Support, N.I.H., Extramural]. *Behavioural Brain Research, 234*(2), 278-284. doi: 10.1016/j.bbr.2012.06.027
Lenox, R. H., Kant, G. J., Sessions, G. R., Pennington, L. L., Mougey, E. H., & Meyerhoff, J. L. (1980). Specific hormonal and neurochemical responses to different stressors. *Neuroendocrinology, 30*(5), 300-308.
Madden, K. S., Szpunar, M. J., & Brown, E. B. (2013). Early impact of social isolation and breast tumor progression in mice. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.]. *Brain, Behavior, and Immunity, 30 Suppl*, S135-141. doi: 10.1016/j.bbi.2012.05.003
Newberry, B. H. (1978). Restraint-induced inhibition of 7,12-dimethylbenz[a]anthracene-induced mammary tumors: relation to stages of tumor development. *Journal of the National Cancer Institute, 61*(3), 725-729.
Newberry, B. H., Frankie, G., Beatty, P. A., Maloney, B. D., & Gilchrist, J. C. (1972). Shock stress and DMBA-induced mammary tumors. *Psychosomatic Medicine, 34*(4), 295-303.
Newberry, B. H., Gildow, J., Wogan, J., & Reese, R. L. (1976). Inhibition of Huggins tumors by forced restraint. *Psychosomatic Medicine, 38*(3), 155-162.
Pajovic, S. B., Pejic, S., Stojiljkovic, V., Gavrilovic, L., Dronjak, S., & Kanazir, D. T. (2006). Alterations in hippocampal antioxidant enzyme activities and sympatho-adrenomedullary system of rats in response to different stress models. [Research Support, Non-U.S. Gov't]. *Physiological Research, 55*(4), 453-460.
Pradhan, S. N., & Ray, P. (1974). Effects of stress on growth of transplanted and 7,12-dimethylbenz(alpha)anthracene-induced tumors and their modification by psychotropic drugs. *Journal of the National Cancer Institute, 53*(5), 1241-1245.
Ray, P., & Pradhan, S. N. (1974). Growth of transplanted and induced tumors in rats under a schedule of punished behavior. *Journal of the National Cancer Institute, 52*(2), 575-577.
Ros-Simo, C., & Valverde, O. (2012). Early-life social experiences in mice affect emotional behaviour and hypothalamic-pituitary-adrenal axis function. [Research Support, Non-U.S. Gov't]. *Pharmacology, Biochemistry and Behavior, 102*(3), 434-441. doi: 10.1016/j.pbb.2012.06.001
Rozeske, R. R., Evans, A. K., Frank, M. G., Watkins, L. R., Lowry, C. A., & Maier, S. F. (2011). Uncontrollable, but not controllable, stress desensitizes 5-HT1A receptors in the dorsal raphe nucleus. [Comparative Study

Research Support, N.I.H., Extramural]. *Journal of Neuroscience, 31*(40), 14107-14115. doi: 10.1523/JNEUROSCI.3095-11.2011
Shively, C. A., Register, T. C., Grant, K. A., Johnson, J. L., & Cline, J. M. (2004). Effects of social status and moderate alcohol consumption on mammary gland and endometrium of surgically postmenopausal monkeys. [Research Support, U.S. Gov't, P.H.S.]. *Menopause, 11*(4), 389-399.
Simpson, J., & Kelly, J. P. (2012). An investigation of whether there are sex differences in certain behavioural and neurochemical parameters in the rat. [Research Support, Non-U.S. Gov't
Review]. *Behavioural Brain Research, 229*(1), 289-300. doi: 10.1016/j.bbr.2011.12.036
Sklar, L. S., & Anisman, H. (1980). Social stress influences tumor growth. [Research Support, Non-U.S. Gov't]. *Psychosomatic Medicine, 42*(3), 347-365.
Sklar, L. S., & Anisman, H. (1981). Stress and cancer. [Research Support, Non-U.S. Gov't]. *Psychological Bulletin, 89*(3), 369-406.
Sterrenburg, L., Gaszner, B., Boerrigter, J., Santbergen, L., Bramini, M., Elliott, E., . . . Kozicz, T. (2011). Chronic stress induces sex-specific alterations in methylation and expression of corticotropin-releasing factor gene in the rat. [Research Support, Non-U.S. Gov't]. *PLoS One, 6*(11), e28128. doi: 10.1371/journal.pone.0028128
Su, F., Ouyang, N., Zhu, P., Ouyang, N., Jia, W., Gong, C., . . . Song, E. (2005). Psychological stress induces chemoresistance in breast cancer by upregulating mdr1. [Research Support, Non-U.S. Gov't]. *Biochemical and Biophysical Research Communications, 329*(3), 888-897. doi: 10.1016/j.bbrc.2005.02.056
Trainor, B. C. (2011). Stress responses and the mesolimbic dopamine system: social contexts and sex differences. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Review]. *Hormones and Behavior, 60*(5), 457-469. doi: 10.1016/j.yhbeh.2011.08.013
Trainor, B. C., Sweeney, C., & Cardiff, R. (2009). Isolating the effects of social interactions on cancer biology. [Comment
Review]. *Cancer Prev Res (Phila), 2*(10), 843-846. doi: 10.1158/1940-6207.CAPR-09-0167
Varela, J. A., Wang, J., Christianson, J. P., Maier, S. F., & Cooper, D. C. (2012). Control over stress, but not stress per se increases prefrontal cortical pyramidal neuron excitability. [Research Support, N.I.H., Extramural]. *Journal of Neuroscience, 32*(37), 12848-12853. doi: 10.1523/JNEUROSCI.2669-12.2012
Volden, P. A., & Conzen, S. D. (2013). The influence of glucocorticoid signaling on tumor progression. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Review]. *Brain, Behavior, and Immunity, 30 Suppl*, S26-31. doi: 10.1016/j.bbi.2012.10.022
Volden, P. A., Wonder, E. L., Skor, M. N., Carmean, C. M., Patel, F. N., Ye, H., . . . Conzen, S. D. (2013). Chronic social isolation is associated with metabolic gene expression changes specific to mammary adipose tissue. [Research Support, N.I.H., Extramural
Research Support, U.S. Gov't, Non-P.H.S.]. *Cancer Prev Res (Phila), 6*(7), 634-645. doi: 10.1158/1940-6207.CAPR-12-0458
Weinberg, J., & Emerman, J. T. (1989). Effects of psychosocial stressors on mouse mammary tumor growth. [Research Support, Non-U.S. Gov't]. *Brain, Behavior, and Immunity, 3*(3), 234-246.
Weintraub, A., Singaravelu, J., & Bhatnagar, S. (2010). Enduring and sex-specific effects of adolescent social isolation in rats on adult stress reactivity. *Brain Research, 1343*, 83-92. doi: 10.1016/j.brainres.2010.04.068
Williams, J. B., Pang, D., Delgado, B., Kocherginsky, M., Tretiakova, M., Krausz, T., . . . Conzen, S. D. (2009). A model of gene-environment interaction reveals altered mammary gland gene expression and increased tumor growth following social isolation. [Research Support, N.I.H., Extramural]. *Cancer Prev Res (Phila), 2*(10), 850-861. doi: 10.1158/1940-6207.CAPR-08-0238

Yee, J. R., Cavigelli, S. A., Delgado, B., & McClintock, M. K. (2008). Reciprocal affiliation among adolescent rats during a mild group stressor predicts mammary tumors and lifespan. [Comparative Study
Research Support, N.I.H., Extramural]. *Psychosomatic Medicine, 70*(9), 1050-1059. doi: 10.1097/PSY.0b013e31818425fb