Abstract

**Background:** Since heavy metal cadmium is an endocrine disrupting chemical, we investigated whether maternal exposure to cadmium during the pregnancy alters mammary tumorigenesis among female offspring. **Methods:** From gestation day 10 to day 19, pregnant rat dams were fed modified American Institute of Nutrition (AIN93G) diet containing 39% energy from fat (baseline diet), or the baseline diet containing moderate (75 µg/kg of feed) or high (150 µg/kg) cadmium levels. Some dams were injected with 10 µg 17β-estradiol (E2) daily between gestation days 10 and 19. **Results:** Rats exposed to a moderate cadmium dose in utero were heavier and exhibited accelerated puberty onset. Both moderate and high cadmium dose led to increased circulating testosterone levels and reduced the expression of androgen receptor in the mammary gland. The moderate cadmium dose mimicked the effects of in utero E2 exposure on mammary gland morphology and increased both the number of terminal end buds and pre-malignant hyperplastic alveolar nodules (HANs), but in contrast to the E2, it did not increase 7,12-dimethylbenz (a) anthracene-induced mammary tumorigenesis. **Conclusions:** The effects of in utero cadmium exposure were dependent on the dose given to pregnant dams: Moderate, but not high, cadmium dose mimicked some of the effects seen in the in utero E2 exposed rats, such as increased HANs in the mammary gland.

**Keywords:** Androgen receptor, cadmium, estradiol, estrogen receptor, in utero exposure, mammary cancer, maternal diet, testosterone

INTRODUCTION

Epidemiological and animal studies suggest that early life exposure to exogenous estrogens or estrogen-mimicking compounds modifies mammary gland development and susceptibility to breast cancer.[1-4] The heavy metal cadmium binds and activates the estrogen receptor (ER)-α and the androgen receptor (AR),[5-7] and an exposure to environmentally relevant doses of cadmium mimics the effects of estrogens on mammary and uterine tissues.[5] Thus, in utero exposure to cadmium might increase later risk of developing breast cancer. This is supported by our observation showing that a dietary exposure to cadmium-containing flaxseed early in life increases the incidence of chemically-induced mammary tumors in rats.[8] The effects of cadmium may...
not be limited to early life, since high urinary cadmium concentrations in adulthood are associated with increased breast cancer risk in several human studies.\textsuperscript{[9-12]}

Humans are exposed to cadmium through several food sources as well as through cigarette smoking.\textsuperscript{[13-16]} Food products accumulate cadmium from pesticide residues and contaminated ground water. Consequently, some foods, such as rice and wheat flour, may have cadmium levels as high as 178 \(\mu\)g/kg of food material. Frequent consumption of these foods could result in exposure levels above the World Health Organization’s (WHO) weekly tolerable intake of 7 \(\mu\)g/kg of body weight.\textsuperscript{[17]} Importantly, cadmium is present in the urine of pregnant women as well as their placental tissue,\textsuperscript{[18,19]} and it has been shown to accumulate in embryonic and foetal tissues.\textsuperscript{[20,21]} Thus, maternal exposure to cadmium during pregnancy impacts the fetus, perhaps by acting as an endocrine disruptor.

The present study was designed to investigate whether \textit{in utero} exposure to cadmium through a maternal diet increases offspring’s later susceptibility to mammary tumorigenesis, similarly than \textit{in utero} exposure to estradiol (E2) is reported to do.\textsuperscript{[22]} In addition, we investigated whether \textit{in utero} cadmium exposure affects biomarkers of breast cancer risk. Accelerated puberty is associated with an increased breast cancer risk,\textsuperscript{[23,24]} and early life exposure to endocrine disruptors affects puberty onset in animal models,\textsuperscript{[25,26]} and human.\textsuperscript{[27,28]} Mammary gland morphology, and perhaps cell proliferation and apoptosis, also are surrogate biomarkers of breast cancer risk.\textsuperscript{[29,30]} In addition, possible changes in the protein levels of ER-\(\alpha\) and AR in the mammary tissue and circulating levels of E2 and testosterone were determined.

Results reported here indicate that maternal exposure during pregnancy to either E2 or cadmium increased incidence of terminal end buds (TEBs) in the mammary epithelium and pre-malignant mammary lesions. Cadmium also increased body weight before puberty and accelerated puberty onset. In addition, it led to an elevation in circulating testosterone levels. Findings obtained in our study raise a concern that maternal cadmium exposure during pregnancy alters mammary gland development and increases breast cancer risk among daughters.

**MATERIALS AND METHODS**

**In utero exposure to dietary cadmium**

Pregnant Sprague Dawley rats, purchased from Charles River Laboratories (Wilmington, DE) arrived on gestation day 7 and were housed singly. Beginning on day 10 of pregnancy, dams were fed one of three American Institute of Nutrition (AIN93G) based diets containing of 190 g corn oil per 1000 g of food material (39% of energy from fat) with no, moderate (75 \(\mu\)g cadmium chloride/kg of food material) or high (150 \(\mu\)g cadmium chloride/kg of food material) cadmium levels. Based upon the typical food intake of pregnant Sprague-Dawley rats,\textsuperscript{[22,31]} these treatment groups received either 2-5 \(\mu\)g cadmium chloride/kg of body weight weekly (moderate dose) or 5-10 \(\mu\)g of cadmium chloride per kg of maternal body weight weekly (high dose). \textit{All in utero} diets were custom made by Harlan Teklad (Madison, WI, USA).

To determine whether the cadmium containing diets mimicked exposure to high estrogen levels \textit{in utero}, the group fed a cadmium-free high fat baseline diet were divided to two additional groups. One received vehicle (corn oil) and the other 10 \(\mu\)g 17-\(\beta\)-E2 (Sigma Aldrich) dissolved in corn oil through daily subcutaneous injections from day 10 through 19 of gestation.

On the day of parturition, all the groups were switched to AIN93G chow, containing no cadmium and 18% fat from corn oil. Two days after birth, female offspring were pooled within each treatment group and randomly assigned to be housed with a dam from that group. Male pups were sacrificed. Each dam nursed a total of 10 female pups. After weaning on postnatal day (PND) 25, the pups were housed in groups of 3-5 animals. On PND 28 and 50, five offspring per group and age were sacrificed and mammary glands and serum were collected for further analysis. Experiments were approved and performed in accordance with the Georgetown University Animal Care and Use Committee and followed all state and federal regulations.

**Body weight gain**

Birth weight was determined by weighing all offspring per litter together, and dividing the total weight by the number of offspring in the litter. Postnatal body weights were determined on several occasions between PND 5 and 50.

**Vaginal opening**

To assess the day of puberty onset, vaginal opening was determined by visually investigating the genital area. Offspring were monitored daily from PND 28 through PND 39 for vaginal opening.

**Tissue collection**

**Mammary tissue collection**

At PND 28 and 50, five offspring per group and age were sacrificed. Mammary tissues were collected for whole mounts (left 4\textsuperscript{th} abdominal gland), immunohistochemistry (left 2-3\textsuperscript{rd} inguinal gland), and immunoblots (right 4\textsuperscript{th} gland). Tissues collected for immunohistochemistry were fixed in...
10% formalin, washed in phosphate buffered saline (PBS), dehydrated in 70% ethanol, and paraffin embedded. Slide sections were 4 μm thick. Sections were then stained with hematoxylin/eosin and imaged on Olympus B × 100 microscope at ×4 and ×20 magnifications.

**Circulating hormone levels**

Blood was collected by cardiac puncture on PND 28 and 50 from rats used for assessing mammary gland morphology. Serum was separated by incubating the blood at room temperature for 20-30 min followed by spinning at maximum speed for 10 min. ELISA kits (Cayman Chemicals) were purchased to measure E2 and testosterone concentrations from purified serum per manufacturer’s instructions.

**Mammary morphometry**

Right 4th abdominal mammary gland, obtained from five rats per group at the ages of 28 and 50 days were processed for whole mounts according to National Institutes of Health (NIH) protocol (mammary.nih.gov). Whole mounts were then scanned into digital images using a Hewlett Packard Scanner and software, and the NIH free-ware program Image J was used for image analysis. TEB number was determined by counting TEBs on the digital images using the cell counter plug-in Image J. Ductal elongation (distance between first lymph node and the tip of the epithelial tree), parenchymal area and fat pad area were quantified using the digitized images and the drawing tool in Image J. The numerical outputs are expressed in pixelated units, called here arbitrary unit.

**Determining estrus stage**

Estrus stage on samples obtained on PND 50 was determined by examining at least 5 fields in the mammary whole mounts using published morphological criteria. Specifically, mammary glands obtained from rats that are in the follicular and early luteal stages have pre-dominantly ductal histoarchitecture, while glands of rats from mid to late luteal phase contain pre-dominantly lobuloalveolar structures.

**Mammary epithelial proliferation and apoptosis**

Formalin fixed, paraffin embedded and sectioned mammary glands, obtained from rats on PND 28 and 50 were used to determine cell proliferation and apoptosis. For proliferation analysis, Ki67 (Abcam ab16667-500) staining using an Agilent Technologies Company envision kit for rabbit (DAKO, K4002) was utilized according to manufacturer instructions. TdT-mediated dUTP-biotin nick end labeling TUNEL analysis to determine apoptosis was performed using ISOL S2100 kit from Chemicon according to manufacturer instructions. Images were obtained on an Olympus B ×100 microscope at ×20 magnification. To quantitate cell proliferation and apoptosis, the number of cells staining brown was assessed in ducts, lobules and TEBs by counting 1,000 cells per structure and per gland.

**Immunoblot for steroid receptors**

Protein from mammary tissue was obtained by homogenizing tissue in Radio-Immunoprecipitation Assay RIPA buffer, incubating for 10 min on ice and then spinning for 10 min at maximum speed at 4°C. Supernatant was collected and placed in fresh eppendorf tubes. Antibodies utilized for immunoblot or immunohistochemistry were purchased from Santa Cruz Biotechnology (Santa Cruz, CA) and they were: ER-α (SC-7207) and AR (SC-18). Densitometry was performed on scanned images using Image J. GAPDH (SC-A14) and β-actin (A2228, Sigma Aldrich, US) were used as loading controls.

**Mammary tumorigenesis**

At PND 50, 25-26 rats per group were administered 10 mg of the mammary carcinogen 7, 12-dimethylbenz (a) anthracene (DMBA) (Sigma Chemical Co., St. Louis, MO) by oral gavage. The carcinogen was dissolved in peanut oil and given in a volume of 1.0 mL. Tumor monitoring began 6 weeks after DMBA administration, and rats were checked weekly for mammary tumors by palpation. Tumor size was measured using a caliper and the length, width, and height of each tumor were recorded. Animals were sacrificed when the tumor burden was approximately 5% of total body weight, as required by our institution. All remaining animals, including those without tumors, were sacrificed 20 weeks after DMBA administration. Endpoints for this study were time to tumor appearance (tumor latency), the average number of tumors per animal (tumor multiplicity), the percentage of rats that developed tumors per experimental group (tumor incidence), and the cumulative size of all tumors divided by the number of animals per group (tumor burden).

**Data analyses**

Univariate and Multivariate analyses of variance (U-ANOVA or MANOVA) followed by Tukey’s post-hoc analysis, were used for most end-points. U-ANOVA was performed when data obtained for the four exposure groups were compared within a single time point, such as tumor latency, or circulating hormone levels on PND 28. MANOVA was used to analyses data generated on PND 50 when estrus stage was included to the analysis as a dependent variable. Repeated measures Multivariate Analysis of Variance (RM-MANOVA) was used to analyze differences in postnatal body weights and tumor burden among the groups. Data on cell proliferation and apoptosis were assessed separately in the ducts, lobules and TEBs, and therefore two-way U-ANOVA was used to determine statistical differences. Differences in the day of
the vaginal opening or the incidence of mammary tumors were calculated by the methods developed by Kaplan and Meier, followed by the log rank test. Differences in final tumor incidence among groups were compared using Chi-square test. All data analyses were performed using the statistical software SPSS. The differences were considered significant if the $P$ value was less than 0.05. All probabilities were two-tailed.

**RESULTS**

**Birth weight and postnatal body weight gain**

Birth weight was not affected by *in utero* exposure to cadmium or E2 (data not shown). Postnatal body weight was elevated in the moderate cadmium group on PND 5 ($P < 0.011$) and PND 35 ($P < 0.019$), compared to the offspring of dams exposed to vehicle during pregnancy [Figure 1a and b]. When the rats reached PND 50, no differences in body weights were seen (data not shown).

**Vaginal opening**

Puberty onset, as determined by the day of the vaginal opening, occurred significantly earlier in the moderate level cadmium than in the vehicle or high cadmium groups ($P < 0.042$) [Figure 1c and d].

**Circulating testosterone and E2 Levels**

Rats exposed to moderate ($P < 0.04$) or high cadmium dose ($P < 0.005$) exhibited higher circulating testosterone levels than the vehicle group [Figure 2a]. E2 levels were not statistically different among the groups [Figure 2c].

![Figure 1](image1.png)

**Figure 1**: (a,b) Postnatal bodyweight development and (c,d) age at the vaginal opening in the offspring of dams exposed to a control diet, a diet containing 75 μM Cd/kg feed (moderate cadmium) or 150 μM Cd/kg feed (high cadmium) between gestation days 10 and 20, or injected s.c. with 10 μg estradiol (E2) daily between gestation days 10 and 19. Means ± S.E.M. are shown, with 30-54 rats per group. (a,b) Compared to the controls, body weights of offspring of moderate cadmium dams were significantly elevated on PND 5 and 35. (d) Percentile of rats per group with vaginal opening between PND 29 and 39 are shown. (c) Survival analysis indicated a significant difference among the groups ($P < 0.042$): Vaginal opening occurred significantly earlier in the moderate cadmium group than in the control or high cadmium groups. Bars marked with a different letter differ from each other at a level of $P < 0.05$. 

4 Journal of Carcinogenesis

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PND 50
Testosterone levels were significantly higher in the high cadmium group than in the vehicle ($P < 0.007$) or E2 group ($P < 0.004$) [Figure 2b]. The difference in E2 levels among the groups was of borderline significance ($P < 0.058$): the highest E2 levels were seen in the high cadmium group, and lowest in the E2 group [Figure 2d].

Mammary gland morphology
PND 28
The number of TEBs was significantly elevated in the offspring of dams fed a diet containing moderate level cadmium ($P < 0.032$) or treated with E2 ($P < 0.018$) during the pregnancy, compared with vehicle controls [Figure 3a]. Ductal elongation; i.e., the distance between the first mammary lymph node and the farthest tip of the epithelial tree, was highest in the E2 exposed offspring, when compared to the vehicle controls ($P < 0.06$), moderate cadmium ($P < 0.002$) and higher cadmium groups ($P < 0.036$) [Figure 3c].

PND 50
Estrus stage controlled analysis found no significant differences in the number of TEBs among the groups at this age, although the pattern was the same as on PND 28; i.e., both moderate cadmium and E2 in utero exposed rats had more TEBs than the high cadmium group [Figure 3d,e]. Ductal elongation and the size of the fat pad and parenchyma area were similar across the four groups [Figure 3, e, f, g, h].

Proliferation (Ki67) and apoptosis (TUNEL)
PND 28
Ki67 did not differ significantly among the groups, indicating that in utero exposures did not modify mammary epithelial proliferation at this age [Figure 4]. However, different structures contained different amounts of proliferating cells ($P < 0.001$). Specifically, cell proliferation was highest in the TEBs and lowest in the ducts (data not shown). The rate of apoptosis did not vary by the structure analyzed, but was different among the groups.

Figure 2: Circulating levels of testosterone (a and b) and estradiol (E2) (c and d) in the offspring on PND 28 and PND 50 of dams exposed to a control diet, a diet containing 75 $\mu$M Cd/kg feed (moderate cadmium) or 150 $\mu$M Cd/kg feed (high cadmium) between gestation days 10 and 20, or injected s.c. with 10 $\mu$g E2 daily between gestation days 10 and 19. Means ± S.E.M. are shown, with 4-5 rats per group. Bars marked with a different letter differ from each other at a level of $P < 0.05$.
Mammary glands of rats exposed in utero to the moderate cadmium dose contained significantly more apoptotic cells than the glands of vehicle exposed rats (P < 0.019) or E2 rats (P < 0.005) [Figure 4].

**PND 50**

When estrus stage and epithelial structure were included to the analysis, cell proliferation was not significantly affected in the mammary glands across the groups [Figure 4]. No differences in cell proliferation in the three different structures were seen, although, similarly to age 28, TEBs contained the highest number of proliferating cells (data not shown). Apoptosis was significantly higher in the mammary glands of rats exposed to high cadmium diet in utero than in the other three groups (P < 0.016) [Figure 4]. Apoptosis levels were similar in TEBs, alveolar structures and ducts (data not shown).

**ER-α and AR protein levels in the mammary gland**

**PND 28**

The levels of expression of the ER-α and AR were low at this age, and therefore we did not attempt to assess possible changes in their expression.

**PND 50**

AR protein levels were significantly lower in the moderate (P < 0.001) and high (P < 0.011) cadmium groups and in the E2 group (P < 0.001) than in the vehicle-exposed offspring, when data were controlled for the estrus stage [Figure 5]. Mammary gland ER-α levels were significantly elevated in the high cadmium (P < 0.004) or E2 groups (P < 0.012) at this age [Figure 5].

**Mammary tumorigenesis**

The number of hyperplastic alveolar nodules (HANs) in the 4th mammary glands of rats at sacrifice; i.e., 20 weeks...
after DMBA exposure was higher in the E2 (P < 0.015) and moderate cadmium groups (P < 0.021) than in the controls [Figure 6a]. The latency to the appearance of the first tumor per animal or tumor multiplicity was not statistically significant among the four groups [Table 1]. The final tumor incidence was 73% in the vehicle group, 80% in moderate cadmium group, 56% in high cadmium group, and 71% in E2-exposed offspring [Figure 6b]. When compared to the vehicle group, tumor burden—the combined volume of tumors per animal—was significantly higher in the E2 group (P < 0.001) [Figure 6c]. In utero E2-exposed rats also exhibited higher tumor burden than the moderate (P < 0.02) or high cadmium (P < 0.051) offspring.

DISCUSSION

In animal models, maternal exposure to E2 during the pregnancy, or dietary factors which elevate maternal hormonal environment, such as a high-fat diet, increases female offspring’s later susceptibility to mammary cancer. We investigated whether an endocrine disruptor cadmium, when given to pregnant rat dams via diet, alters mammary tumorigenesis among offspring. Two different doses of cadmium were used: moderate cadmium containing 75 μg CdCl2/kg feed and high cadmium containing 150 μg CdCl2/kg. Based on the average daily food intake of pregnant Sprague-Dawley rats, the moderate dose is likely to have resulted maternal exposures within levels deemed acceptable by WHO; i.e., 2–5 μg cadmium/kg of maternal body weight weekly, whilst the higher cadmium dose is estimated to yield cadmium exposure levels of 5–10 μg/kg of body weight weekly, which might have led to cadmium intake that exceeded the weekly tolerable intake of cadmium (7 μg/kg of body weight).

Our results indicated that a maternal dietary exposure to the moderate cadmium dose during the pregnancy increased female offspring’s susceptibility to develop mammary HANs, which are precursors of malignant mammary lesions. However, this exposure did not significantly increase mammary tumorigenesis as determined by assessing mammary tumor latency, incidence, multiplicity or burden. An exposure to the higher level of cadmium through a maternal diet had no effect on HANs or mammary cancer risk. Other endocrine disruptors have been reported to have similar dose-dependent effects: Mice exposed neonatally to low levels of the synthetic estrogen diethylstilbestrol (DES) subsequently exhibit enhanced responsiveness of the uterus to E2, whilst

![Figure 4: (a) Representative examples of positive staining for Ki67 antibody (proliferation) and TUNEL analysis (apoptosis) are shown at both ages. (b) Changes in mammary cell proliferation (assessed using Ki67 antibody) and apoptosis (assessed using TUNEL) in the mammary glands on PND 28 and 50 in the offspring of dams exposed to a control diet, a diet containing 75 μM Cd/kg feed (moderate cadmium) or 150 μM Cd/kg feed (high cadmium) between gestation days 10 and 20, or injected s.c. with 10 μg estradiol daily between gestation days 10 and 19. Means ± S.E.M. are shown, with 5 rats per group. Bars marked with a different letter differ from each other at a level of P < 0.05.](image)

<table>
<thead>
<tr>
<th>In utero exposures</th>
<th>Number rats/number of tumors with tumors</th>
<th>Final tumor incidence (%)</th>
<th>Latency (weeks)</th>
<th>Multiplicity (number of tumors/rat)</th>
<th>Final tumor burden (total tumor volume per group)</th>
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<tr>
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<td>26/19</td>
<td>73%</td>
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<td>High cadmium</td>
<td>25/14</td>
<td>56%&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>E2</td>
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<td>71%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.8±0.8</td>
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<td>1204.4&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup>In utero exposure groups marked with different letters are significantly different from each other (P<0.05), E2: Estradiol

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**Figure 4:** (a) Representative examples of positive staining for Ki67 antibody (proliferation) and TUNEL analysis (apoptosis) are shown at both ages. (b) Changes in mammary cell proliferation (assessed using Ki67 antibody) and apoptosis (assessed using TUNEL) in the mammary glands on PND 28 and 50 in the offspring of dams exposed to a control diet, a diet containing 75 μM Cd/kg feed (moderate cadmium) or 150 μM Cd/kg feed (high cadmium) between gestation days 10 and 20, or injected s.c. with 10 μg estradiol daily between gestation days 10 and 19. Means ± S.E.M. are shown, with 5 rats per group. Bars marked with a different letter differ from each other at a level of P < 0.05.
Figure 5: Protein expression of AR and ER-α in the mammary glands on PND 50 in the offspring of dams exposed to a control diet, a diet containing 75 µM Cd/kg feed (moderate cadmium) or 150 µM Cd/kg feed (high cadmium) between gestation days 10 and 20, or injected s.c. with 10 µg estradiol daily between gestation days 10 and 19. Means ± S.E.M. are shown, with 4-5 rats per group. Bars marked with a different letter differ from each other at a level of $P < 0.05$.

Figure 6: Changes in dimethylbenz (a) anthracene-induced mammary tumorigenesis in the offspring of dams exposed to a control diet, a diet containing 75 µM Cd/kg feed (moderate cadmium) or 150 µM Cd/kg feed (high cadmium) between gestation days 10 and 20, or injected s.c. with 10 µg estradiol daily between gestation days 10 and 19. (a) Number of hyperplastic alveolar nodules in the 4th mammary gland of 5-7 rats per group. Means ± S.E.M. are shown. Bars marked with a different letter differ from each other at a level of $P < 0.05$. (b) Cumulative mammary tumor incidence. (c) Cumulative mammary tumor burden; significantly different between E2 and vehicle ($P < 0.001$), moderate cadmium ($P < 0.02$), and high cadmium ($P < 0.051$).

A high neonatal DES exposure has an opposite effect. Therefore, the same compound can have different effects on disease-related endpoints, depending on the level of exposure.

In women, high cadmium levels are associated with the elevated testosterone levels. In agreement with this report, we found that maternal exposure to either moderate or high cadmium levels (but not to E2) during the pregnancy led to an increase in circulating testosterone levels among the offspring. Androgens inhibit AR expressing human breast cancer cell proliferation in vitro and induce apoptosis through this receptor. Our data support these observations and show that AR levels were reduced in the mammary glands of in utero cadmium exposed rats, and apoptosis was increased.

However, the association between androgen levels, AR and breast cancer remains unclear. Studies carried out using in vivo animal models indicate that androgens inhibit the growth of mammary tumors. As mentioned above, androgens inhibit the growth of human breast cancer cells in vitro. In contrast, human studies indicate that elevated testosterone levels are associated with an increase in pre- and post-menopausal breast cancer risk. It has been suggested that AR signaling inhibits proliferation of ER positive...
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