Review

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Environmental Enrichment in Cancer: A Possible Tool to Combat Tumor Development: A Systematic Review

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Abstract: *Aims:* This systematic review aims to evaluate the influence of Environmental Enrichment (EE) on oncological factors in experimental studies involving various types of cancer models. *Methods:* A comprehensive search was conducted in three databases: PubMed (161 articles), Embase (335 articles), and Scopus (274 articles). Eligibility criteria were applied based on the PICOS strategy to minimize bias. Two independent researchers performed the searches, with a third participant resolving any discrepancies. The selected articles were analyzed, and data regarding sample characteristics and EE protocols were extracted. The outcomes focused solely on cancer and tumor-related parameters, including cancer type, description of the cancer model, angiogenesis, tumor occurrence, volume, weight, mice with tumors, and tumor inhibition rate. *Key-findings*: A total of 770 articles were identified across the three databases, with 12 studies meeting the inclusion criteria for this systematic review. The findings demonstrated that different EE protocols were effective in significantly reducing various aspects of tumor growth and development, such as angiogenesis, volume, weight, and the number of mice with tumors. Furthermore, EE enhanced the rate of tumor inhibition in mouse cancer models. *Findings:* This systematic review highlights the significant impact of EE protocols on multiple parameters associated with tumor growth and development, including angiogenesis, occurrence, volume, weight, and the tumor incidence. Moreover, EE demonstrated the potential to increase the rate of tumor inhibition. These findings underscore the importance of EE as a valuable tool in the management of cancer.

Keywords: enriched environment; cancer; tumor growth; angiogenesis; pro-oncogenic factor

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Introduction

Environmental Enrichment (EE) is an enhanced mental stimulation method that promotes stimuli developing memory-demanding tasks due to socio-environmental context where the rodents can interact actively with their complex surroundings [1,2]. In this context, EE has been investigated in animal studies and considers several disorders, such as Alzheimer's disease, Parkinson's disease, Stroke, and anxiety-like and depression-like behaviors [3–5]. Therefore, EE is known to delay the rate of progression and/or reduce the symptoms, and the severity of these diseases. Also, evidence has shown an enhancement in immune function due to EE, mitigating inflammatory disorders, a risk factor that predisposes to the development of chronic diseases, such as cancer [6].

Cancer consists of a complex of 200 diseases. It is known that dysfunctional immune response and inflammation have a considerable impact on cancer development and its progression [7]. Moreover, studies have shown that adjuvant cancer treatment induces a permanent systemic inflammatory state, associated with high levels of inflammatory cytokines, and weaknesses in physical function [8]. Also, cancer treatment is often associated with psychological distress, chronic pain, cachexia, fatigue, and long-term impaired quality of life, which are related to the worse general picture of the disease and, consequently, worse prognosis [9].

Recent studies have demonstrated the effect of EE protocols on different types of cancer. In this sense, it has been shown that EE could decrease tumor growth of melanoma, colon, and intestinal cancers [10,11]. Recently, Queen et al. (2021) observed that EE mitigated Lewis Lung Carcinoma growth. Also, it has promoted alterations in markers of proliferation and angiogenesis of Lung Carcinoma [12]. Despite that, the impact of different EE protocols on cancer studies is still not completely clear. In this sense, this systematic review aims to evaluate the influence of EE on tumor factors in experimental models of cancer. We hypothesize that different EE protocols will be able to promote positive changes in parameters related to tumor growth and development.

Methods

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Study Selection and Eligibility Criteria

Eligibility criteria were previously selected to minimize the risk of bias. The inclusion and exclusion criteria followed the PICOS (**P**opulation / **I**ntervention/ **C**ontrol/ **O**utcomes/ **S**tudy) (Table 1). There were no restrictions on language or publication date. Articles that did not meet the following eligibility criteria were excluded **(a)** Studies that used only mice and rats from different species; **(b)** Animals submitted to intervention with different protocols of environmental enrichment, **(c)** Do not have a control group; **(d)** Studies that did not perform a model of cancer and did not evaluate tumor parameters were excluded, as well as review publications, letter, duplicates, and presence of data used in different studies were excluded.

Table 1. PICOS strategy.

	Inclusion Criteria	**Exclusion Criteria**
Population	Rodents	Non-Rodents
Intervention	Environmental enrichment	Non-Environmental enrichment

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Control	Non-Environmental enrichment	Any other comparison group
Outcomes	Type of cancer; cancer model description; Angiogenesis; Tumor Occurrence; Tumor Volume (%, cubic millimeters); Tumor Weight (milligrams, grams) Mice with Tumor and Inhibition (%); Tumor Size (square millimeters).	No Tumor Parameters
Study Design	Animal Studies	Reviews; Case report; Letter to editor; comments, etc.

Information Sources and Search Strategy

The search strategy was carried out during the period from December to January 2023. The databases used were PubMed (Medline), Scopus, and Embase. The search strategies used were PubMed (Medline), Embase, and Scopus: (("Environmental Enrichment") OR ("Enriched Environment")) AND ((((((Tumor) OR (Tumors)) OR (Cancer)) OR (Cancers)) OR (Neoplasm)) OR (Malignant Neoplasms)). Filters were also used in the databases: [Species, Animals, and type of publication]

Selection and Data collection process

The screening of studies was performed by reading the title, abstract and full text. The selection of studies was performed by two independent researchers (MSSF and GCJS). Discrepancies were resolved by a third rater. Data were extracted through two independent researchers. Discrepancies were resolved by a third rater (TOF), Figure 1.

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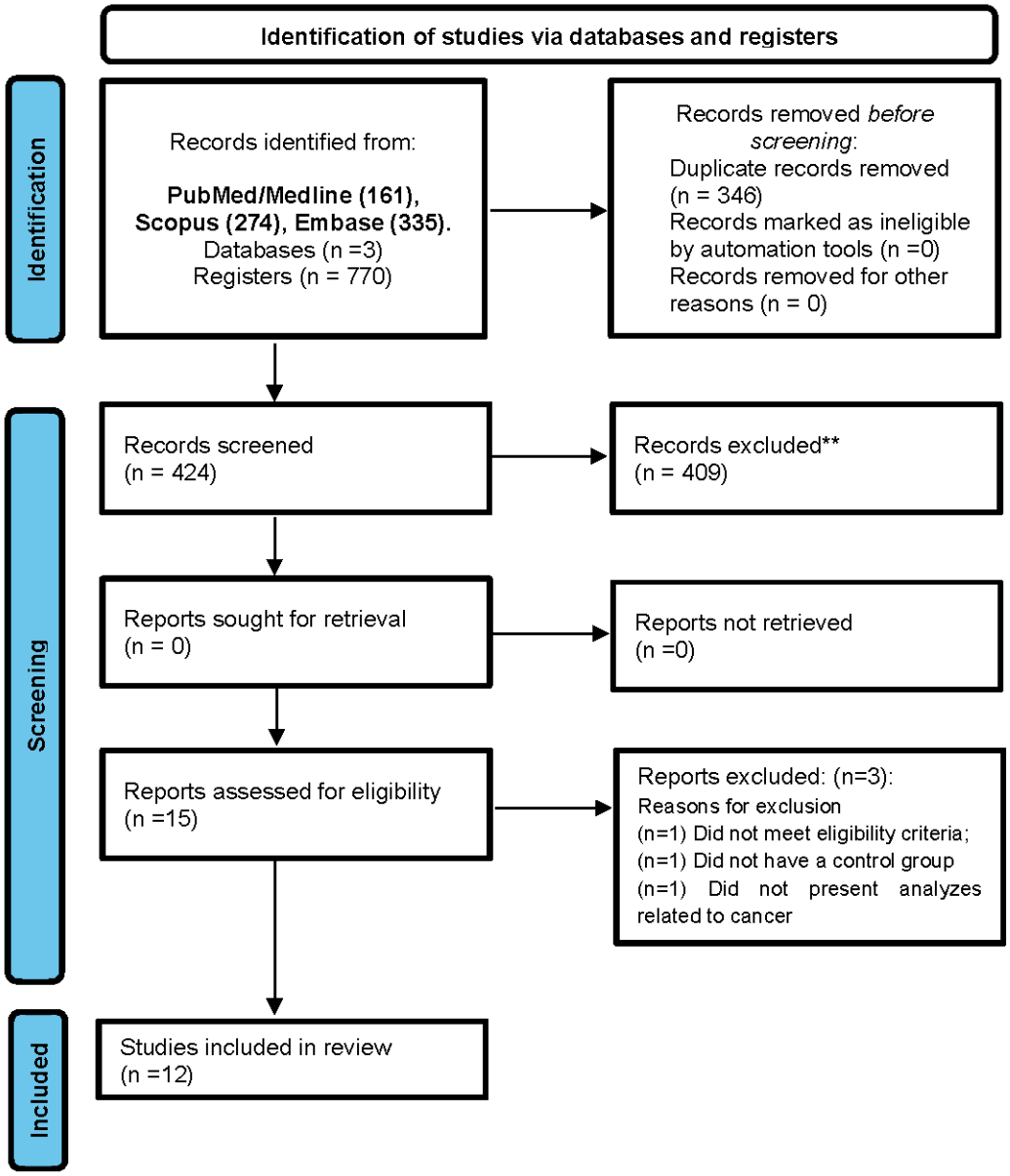

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Data items

Data were extracted about the study (Author and year), Animal characteristics (Species, sex, age), information on the number of animals per cage; Environmental Enrichment Protocol, and Housing dimensions (Length, Width, and Depth or Height, in centimeters or meters). In addition, the exposure time of the environmental enrichment in weeks was collected. In the absence of information, data were not considered. Data were collected on: **Cancer and Tumor outcomes**: Type of cancer; cancer model description; Angiogenesis; Tumor Occurrence; Tumor Volume (%, cubic millimeters); Tumor Weight (milligrams, grams) Mice with Tumor and Inhibition (%); Tumor Size (square millimeters).

Methodological Quality Assessment

The SYRCLE's strategy was used to assess the methodological quality of the animal studies. The tool consisted of ten (10) questions that evaluate methodological criteria: Q1- Was the allocation sequence adequately generated and applied? Q2- Were the groups similar at baseline or were they adjusted for confounders in the analysis? Q3- Was the allocation to the different groups adequately

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concealed? Q4- Were the animals randomly housed during the experiment? Q5- Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment? Q6- Were animals selected at random for outcome assessment? Q7- Was the outcome assessor-blinded? Q8- Were incomplete outcome data adequately addressed? Q9- Are reports of the study free of selective outcome reporting? Q10- Was the study free of other problems that could result in a high risk of bias? Questions were answered with options of 'Yes', 'No', or 'Not clear'. When the answer was 'yes', a score was given; when the answer was 'no' or 'not clear', no score was given. The overall scores for each article were calculated as a score of 0-10 points, with the quality of each study being classified as high (8-10), moderate (5-7), or low (<5). The two reviewers independently reviewed all included studies. Discrepancies between evaluators were resolved by consensus. The quality outcomes are described in Table 4**.**

Results

Search Results

In an initial search, 770 articles were found, of which 346 duplicates were excluded was performed with the help of the EndNote software. Then, 424 articles were screened and submitted to the eligibility criteria, and 409 articles were excluded based on title and abstract reading. 15 studies remained for full-text reading, and of these 3 studies were excluded. Finally, 12 studies were included in this systematic review (Figure 1).

Methodological Quality Assessment

The quality analysis of the studies is shown in Table 4. All studies showed adequate and randomized allocation with randomly selected animals. Furthermore, incomplete results were handled appropriately, free from selective results and bias. Because these are studies with intervention with a cancer model, it is not possible to consider the investigation and analysis of the results blind. In general, all studies presented good quality criteria.

Study Characteristics

The included studies were published between 2010 and 2021. In the characteristics of the animals, we observed that all included studies used mice, of different species. Ten studies were performed with C57BL6 mice only [10,12–20]. One study used C57BL6 and BALB/c mice [21] and another B6C3F1 [22]. Eight included studies used male mice and their age ranged from 2-56 weeks. Within the characteristics of the different protocols, we observed that the number of animals per cage ranged from 4-25 animals. In the objects used to establish the EE, great diversity was observed (Huts; Igloo; Running Wheels; Wood toys, among others). The dimension of the cages in Length, Width, and Depth or Height, are expressed in centimeters or meters in these variables. Finally, the duration in weeks of exposure to the EE ranged from 3 to 16 weeks (Table 2).

Table 2. Sample description and characterization of environmental enrichment protocols.

Author, Year	Species, Sex and Age	Animals per Cage	Environmental Enrichment Protocol and Housing dimensions (Length, Width and Depth or Height)	Exposure time to Environmental Enrichment
Bice et al.2017	C57BL6 mice; Female and Male; 16 wks old	15-20	Huts; Mouse Igloo; Rafters; Running Wheels; Tunnel; 15 cm x 20 cm x 29 cm	Short and Long term (16 wks)
Cao et al. 2010	C57BL6 mice; Male; 3 wks old	18-20	Igloos; Huts; Maze; Nesting material; Retreats; Running Wheels; Tunnels; Wood Toys; 1.5 m x 1.5 m x 1.0 m	3-6 wks
Foglesong et al.2019	C57BL6 transgenic mice; Female; 6 wks old	5	Igloos; Huts; Maze; Nesting material; Retreats; Running Wheels; Tunnels; Wood Toys; 63 cm x 49 cm x 44 cm	4 wks
Garofalo et al. 2014	C57BL6 mice; Male; 3 wks-2 months old	10	Climbing Ladders; Seesaws; Running Wheel; Balls; Plastic; Wood; Cardboard Boxes and Nesting material; 36 cm x 54 cm x 19 cm	5 wks
Kappes et al.2012	C57BL6 mice; Female; 3 wks old	10	Running Wheel; Tunnels; Igloos; Nesting material and Wooden Toys; 60 cm x 38 cm x 20 cm	16 wks
Li et al.2015	C57BL6 mice; Male; 3 wks old	12	Running Wheel; Small Huts; Tunnels; Wood Toys; and Nesting materials; 61cm x 43 cm x 21 cm	3-5 wks
Li et al.2021	C57BL/6 mice; Male; 2–3 wks old and BALB/c mice; male; 3 wks old	8-25	Running Wheels; Tunnels; Huts; Retreats; and Wood Toys; 40 cm x 30 cm x 20 cm	3-10 wks
Queen et al.2021	C57BL6 mice; Female; 3 and 14 months old	10	Running Wheels; Huts; Shelters; Toys; Tunnels; Maze; and Nesting material; 120 cm x 90 cm x 76 cm	11 wks
Takai et al.2016	B6C3F1 mice; Female; 6 wks old	12-24	Mouse Igloos; 218 mm x 320 mm x 133 mm	6 wks-100 days
Watanabe et al.2019	C57BL/6 mice; male; 24-35 wks old	4-14	Mouse Igloos and Fast -Trac; 21.8 cm x 32 cm x 13.3 cm	10-14 wks

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Westwood et al.2013	C57BL/6 mice; male; 3 wks old	20	Exercise Wheels; Cardboard Boxes; PVC Tubes; Plumbing T Piece; 81 cm x 57 cm x 34 cm	6 wks
Wu et al.2016	C57BL/6 mice; male; 3 wks old	12	Exercise Wheels; Tunnels; Wood Toys; Plastic Tubes; 61cm x 43 cm x 21 cm	3 wks

Legend: Cm: Centimeters; m: meters; mm: millimeters; wks: weeks.

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Types and Cancer Models

Different types of cancer were used within the included studies: breast cancer [14,19], lung cancer [12,20], pancreatic cancer model [13,17], melanoma [10,15], glioma [16], liver cancer [21] and another ovary cancer [22]. In the cancer models used in the included studies, we identified the mimicry of cancer models by injection/inoculation of cancer cells subcutaneously in nine included studies.

Tumor Volume, Weight, Size, and Angiogenesis After Environmental Enrichment

Eight included studies evaluated tumor volume is usually measured using the equation (Volume = length x width^2 x /6) and it was expressed in mm^3 and percentage [10,12–14,16,18,19,21]. The results showed that EE was able to significantly reduce tumor volume in mice with colon, melanoma, breast, glioma, pancreatic, liver, and lung cancer. Additionally, eight included studies evaluated tumor weight expressed in milligrams, grams, and percentages. [10,12–14,17,18,20,21]. Seven studies demonstrated a decrease in tumor weight after EE in mice with melanoma, breast, glioma, pancreatic, liver, and lung cancer [10,12–14,17,20,21], only 1 study did not show significant differences [18]. One study only analyzed tumor size [15] and did not observe significant differences after EE. One study only analyzed angiogenesis, in this sense, a significant reduction was observed after EE [18], Table 3. Therefore, it is observed that EE was able to act positively on the oncological variables analyzed in the included studies (Figure 2).

Table 3. Cancer types, model and impacts of environmental enrichment on tumor outcomes in experimental models.

Author, Year	Type of Cancer	Cancer model	Tumor outcomes
Bice et al.2017	Colon Tumor	Genetically induced by mutant's phenotypes (A*pc*^{Min} and Apc^{Min} Tcf4^{Het})	↓ Tumor Angiogenesis; Volume (mm^3); ↔ Tumor number and Weight (mg)
Cao et al.2010	Melanoma	Implanted subcutaneously in the flank (B16F10 syngeneic melanoma cell line / 1 x 10^5 per mouse).	↓ Tumor volume (% and mm^3); Tumor Weight (%); ↔ Tumor occurrence (%); Mice with tumor (%)
Foglesong et al.2019	Breast Tumor	Inoculation of 50.000 breast cancer cells derived from MMTV-PyMT mice in 100 µL serum-free in the right mammary	↓ Tumor occurrence (%) and Volume (mm^3)
Garofalo et al.2014	Glioma	Were injected intracranially GL261 or CD133$^+$-GL261 (7.5 x 10^4), and U87MG (5 x 10^4) glioma cells	↓ Tumor volume (% and mm^3); ↔ Mice with tumor
Kappes et al.2012	Breast Tumor	Mammary cell line EO771 (56105 cells in 100 ml) were transplanted subcutaneously into the fourth right mammary fat pad	↓ Tumor volume (mm^3); Weight (mg)
Li et al.2015	Pancreatic	Subcutaneous tumors were prepared and implanted using Panc02 cells (6 x 10^5 per mouse) in their right flank	↓ Tumor volume (mm^3); Weight (g); ↑ Tumor Inhibition (%)
Li et al.2021	Liver	Murine HCC cells (Hepa1-6, H22 and LPC-H12) were transplanted subcutaneously and injected into the right flanks of mice (~5 × 10^5–1 × 10^6) cells	↓ Tumor occurrence; Volume (mm^3); Weight (g)
Queen et al. 2021	Lung	LLC cells (2.5 x 10^5) were implanted in mouse subcutaneous tissue with 100 µL of serum-free	↓ Tumor volume (mm^3); Weight (g)

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Takai et al.2016	Ovarian	OV3121 cells, derived from an ovarian granulosa cell tumor (5×10^5 cells) were injected subcutaneously onto the back of the mice	↓ Mice with tumor (%)
Watanabe et al.2019	Lung	3LL tumor cells (5×10^4) were injected subcutaneously in the right flanks to develop solid intra-abdominal tumors. Alternatively, 3LL cells (1 × 105) were injected into the tail vein to form colonies of metastatic cells	↓ Tumor Weight (g), and Occurrence
Westwood et al.2013	Melanoma	Were inoculated subcutaneously with 100 µl of a single-cell suspension of 1×10^5 B16F10 melanoma cells	↔ Tumor Size (mm^2)
Wu et al.2016	Pancreatic	Panc02, Panc02-VC or Panc02-ABCA8b cells (6 $x10^5$ per mice) were implanted subcutaneously in the right flank	↓ Tumor Weight (g), ↑ Tumor Inhibition (%)

Legend:g:grams; HHC: cellular hepatocellular carcinoma; LLC: Lewis Lung Carcinoma; mm^2:square millimeters; mm^3: cubic millimeters; mg:miligrams; mL: milliliters; µL: microliter; % percentage; ↔: No significant difference (p>0.05).

Table 4. Methodological Quality Assessment.

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Bice et al., 2017	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Cao et al., 2010	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Foglesong et al., 2019	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Garofalo et al., 2014	Y	U	Y	Y	N	Y	N	Y	Y	Y
Kappes et al., 2012	Y	Y	Y	Y	N	Y	N	Y	Y	Y

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Li et al., 2015	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Li et al., 2021	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Queen et al., 2021	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Takai et al., 2016	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Watanabe et al., 2019	Y	Y	Y	Y	N	Y	N	Y	Y	Y
Westwood et al. 2013	Y	U	Y	Y	N	Y	N	Y	Y	Y
Wu et al., 2016	Y	Y	Y	Y	N	Y	N	Y	Y	Y

Legend: Q1. Was the allocation sequence adequately generated and applied? Q2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?; Q3. Was the allocation to the different groups adequately concealed during? Q4. Were the animals randomly housed during the experiment?; Q5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?; Q6. Were animals selected at random for outcome assessment?; Q7. Was the outcome assessor blinded?; Q8. Were incomplete outcome data adequately addressed?; Q9. Are reports of the study free of selective outcome reporting?; Q10. Was the study apparently free of other problems that could result in high risk of bias?; Y, Yes; N, No; U, Unclear

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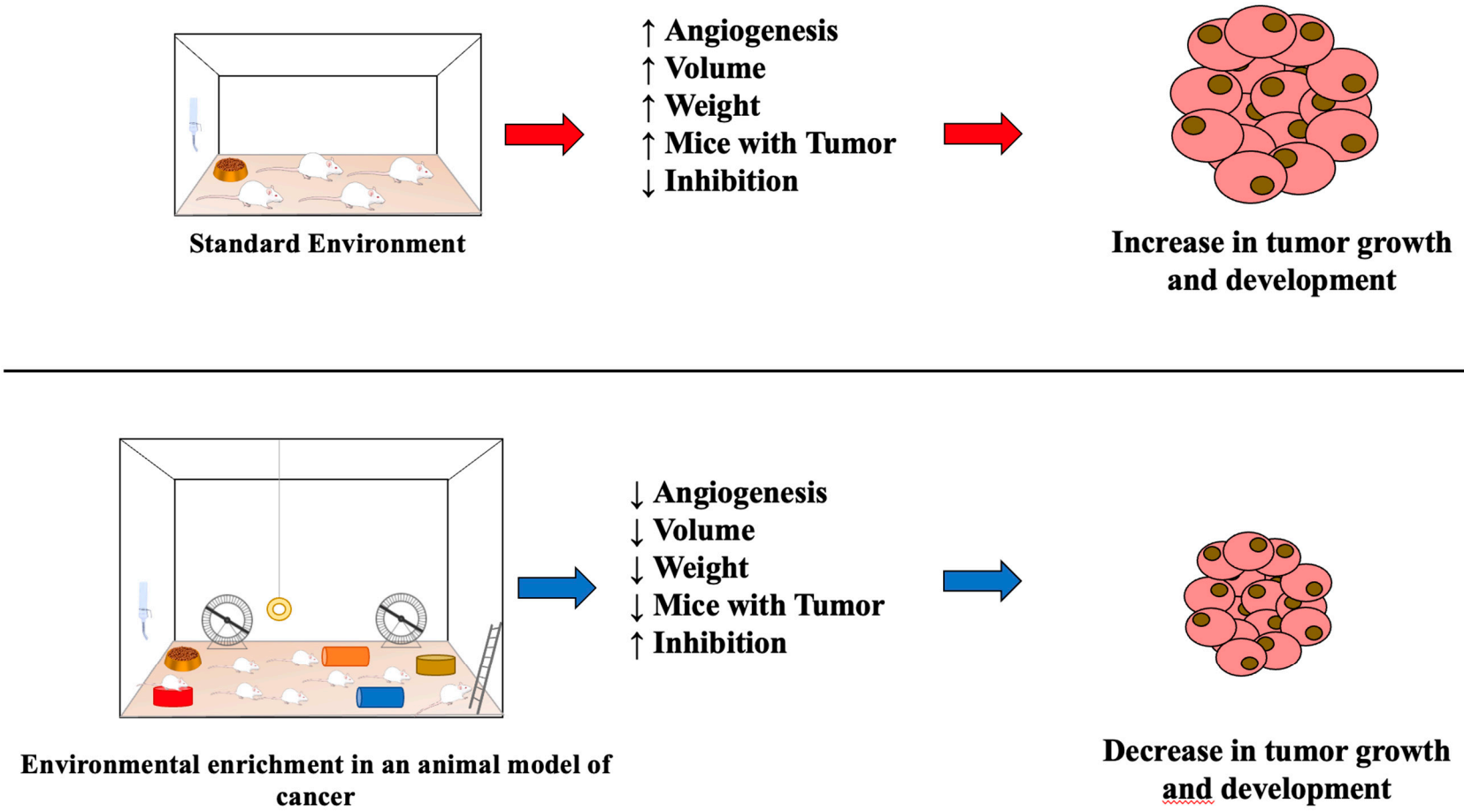

Figure 2. Impacts of environmental variability (standard environment and environmental enrichment) on parameters related to tumor growth and development and experimental models of cancer.

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Tumor Number, Occurrence, Inhibition, and Mice with Tumor after different protocols of environmental enrichment

One study analyzed tumor numbers and did not identify significant differences after environmental enrichment [18]. Four studies evaluated the occurrence of tumors in mice, and a significant reduction was observed after EE in melanoma, breast, liver, and lung cancer models [10,19–21]. On the other hand, two studies only evaluated the percentage inhibition of tumors [13,17]. In this sense, an increase in tumor inhibition in percentage was observed after the intervention with EE. Three included studies analyzed the percentage of mice affected by tumors [10,16]. Two studies did not observe significant differences in the prevalence of tumors [16,18]. However, one study only observed a reduction in the number of tumors in mice after environmental enrichment in an ovarian cancer model [22]. Thus, it is evident that exposure to EE was able to significantly reduce the number of tumors and their occurrence, as well as increase tumor inhibition in mice (Figure 2).

Discussion

The findings of this systematic review demonstrate that the implementation of EE protocols has a significant impact on multiple parameters associated with tumor growth and development. Notably, EE was found to reduce tumor volume, weight, angiogenesis, tumor cell number, occurrence, and the presence of tumors in mice. These observations have important implications for understanding the potential antitumor activity of EE.

Tumor volume and weight are widely recognized as reliable indicators of tumor progression and treatment efficacy in different tumor types, including colon, breast, glioma, pancreatic, liver, and lung cancers [23]. The present review found evidence suggesting that EE exerts its antitumor effects through hormonal mechanisms including a decrease in cortisol levels and the modulation of sympathetic activity.

Studies by Kamiya et al. (2021) have highlighted the significant role of sympathetic nerves in cancer progression, particularly under conditions of stress. Evidence has been shown that the sympathetic nerves must innervate the tumor microenvironment, promoting cancer cell alterations, and angiogenesis, but also altering immune cells' response to the cancer environment. In this regard, experimental studies have observed that chemical and surgical sympathectomy might suppress carcinogenesis from tumor initiation and its progression [24]. Moreover, Magnon et al. (2013) have found that genetic deletion of stromal β2- and β3-adrenergic receptors can prevent prostate cancer development in early phases [24]. This underscores the importance of stress management and the regulation of sympathetic pathways as potential strategies to exert antitumor effects [23]. Furthermore, the ability of EE to influence tumor volume makes it a potential tool for monitoring the effectiveness of radiotherapy, as suggested by Dubben et al. (1998) [25]. No significant differences were observed in tumor size after EE.

Angiogenesis, the formation of new blood vessels, is critical for tumor establishment and maintenance. Vascular endothelial growth factor (VEGF) has emerged as a key mediator of tumor angiogenesis, promoting tumor growth, invasion, and metastasis [26,27]. Targeting VEGF and other biological agents involved in angiogenesis has been explored as a therapeutic strategy to limit oxygen and nutrient supply to tumors [28]. In this regard, EE has been shown to reduce tumor angiogenesis, suggesting its potential as a non-pharmacological approach to inhibit this process [18]. The depletion of vessels, vessel normalization, and immune activation are potential pathways through which EE may exert its anti-angiogenic effects [29]. Queen et al. (2021) have noticed that EE promoted inhibition of mRNA expression in a variety of markers of angiogenesis, such as *COX2* and *VEGF* genes [12]. Furthermore, EE has been found to regulate natural killer cells, demonstrating its immunoprotective role against cancer [30]. Encouraging the adoption of lifestyle factors such as EE, physical activity, and nutritional adjustments may further modulate tumor angiogenesis [31,32]. Besides the relevance that tumors exhibited alterations in angiogenesis due to EE, the mechanism by which EE promotes the inhibition of angiogenesis is unknown.

This systematic review also examined the effects of EE on tumor cell number, occurrence, inhibition, and the presence of tumors in mice. Consistent with the present findings, Di Castro et al. (2021) reported a reduction in glioma tumor cell proliferation in mice exposed to EE [33]. This effect may be mediated by a decrease in GABAergic activity in the peritumoral area [34]. The neurotransmitter GABA derived from B cells has been shown to promote the differentiation of monocytes into anti-inflammatory macrophages and inhibit the action of CD8+ T cells [34]. Therefore, the inactivation of GABAergic activity appears to enhance antitumor responses. Additionally, increased brain-derived neurotrophic factor (BDNF) production stimulated by EE has been linked to reduced tumor growth in gliomas. BDNF expression has also been associated with enhanced maturation of natural killer cells in various tissues [35]. The findings of this systematic review highlight the beneficial effects of EE protocols on various parameters related to tumor growth and development. EE demonstrates the potential to reduce tumor volume, weight, angiogenesis, and tumor occurrence.

Strengths and limitations

The present study stands out for being the first systematic review that compiled the impacts of EE protocols on different parameters related to tumor growth and development in experimental models of cancer. Furthermore, these systematically complied the evidence in experimental models of cancer in mice suggests that non-pharmacological tools could be increasingly incorporated and tested as adjuvant treatment in various types of cancer. The sensitivity of tumor growth and development to psychophysiological stress justifies the use of EE, which is increasingly being consolidated as a low-cost, viable, reproducible, and reliable tool capable of promoting voluntary stimulation of cognitive, motor, and somatosensory domains, culminating in the reduction of stress-linked signaling pathways including the pituitary, pituitary-adrenal axis through regulation of sympathetic nervous system activation. A higher level of translational evidence aimed at understanding the different mechanisms and responses produced by EE in the effective regulation of tumorigenesis, helping to develop new therapeutic strategies. Within the limitations presented by this systematic review, we highlight the low variability of rodent species used in the included studies where they mainly used C57BL6. A higher number of rodent species would help in understanding the impacts of EE and cancer within the diversity and individuality of each organism, leading to the observation of divergences and similarities of each regulatory mechanism of tumor development.

Conclusions

In conclusion, our findings strongly support the effectiveness of environmental enrichment (EE) protocols in mitigating various parameters associated with tumor growth and development. Through EE interventions, we observed significant reductions in angiogenesis, tumor occurrence, volume, weight, and the cells number of mice with tumors. Notably, EE also demonstrated the potential to enhance tumor inhibition rates. These findings offer valuable insights into the therapeutic landscape, suggesting that incorporating EE protocols alongside conventional cancer treatments may yield substantial benefits. EE can potentially complement existing therapies by providing a non-pharmacological means to regulate tumor growth and progression. Moving forward, further research is warranted to unravel the underlying molecular mechanisms through which EE exerts its antitumor effects. Exploring these pathways will enable the development of more targeted and personalized EE interventions, enhancing their clinical efficacy and applicability in translational studies, thus better understanding the responses of environmental enrichment in different models and types of study.

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