

# A Study of Chemotherapy-Related Cognitive Impairment in Gynecologic Cancer Patients

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## Abstract

**Objectives:** 1) To evaluate post-chemotherapy cognitive functions in gynecology oncology patients; 2) To analyze the factors that influence memory impairment in those patients. **Methods:** The experimental group (Group A) consisted of 53 patients admitted between year 2009-2011, with age ranging from 18 - 66 years old, suffering from cervical cancer (n = 22), ovarian cancer (n = 24), and other gynecologic cancer types grouped together (n = 7), treated with adjuvant TP regimen chemotherapy (n = 47) or other regimen chemotherapy grouped together (n = 6). The chemotherapy patients are grouped according to their age (pre-perimenopausal <45 years old and post-perimenopausal period ≥45 years old), education level (lower educated of less than 9 years of education and higher educated of more than 9 years of education), types of cancer (cervical cancer, ovarian cancer, other cancer), types of chemotherapy regimen received (TP regimen, other regimen). The control group is divided into 2 groups, non-chemotherapy patients (Group B) and healthy controls (Group C). According to patients' chemotherapy is divided into five group, control group is divided into 2 groups. Using two subjective questionnaires (Everyday Memory Questionnaires and CAMDEX) and 1 objective problems Test (Random Number Test), right and wrong points according to the problem, determine subjects of cognitive function damage. Problems before test in patients who did not receive any treatment (T1) and patients received two or more than 3 to 4 weeks after chemotherapy regimen (T2) after the test. The patient test results comparing with control group. **Results:** 1) The data show that chemotherapy patients have more cognitive problems than chemotherapy patients and healthy controls. 2) Found in its own control study before and after chemotherapy, the cognitive dysfunction after chemotherapy and before chemotherapy is statistically significant (p = 0.039). 3) Gynecological cancer after chemotherapy in patients with cognitive dysfunction, and in the scarf premenopausal and postmenopausal group, has statistical difference (p = 0.031). 4) Gynecological cancer after chemotherapy in patients with cognitive dysfunction, and in the cultural level between high and low degree of cultural groups, is statistically significant (p = 0.010). 5) Gynecological cancer after chemotherapy in patients with cognitive dysfunction, between cervical cancer and ovarian cancer group, has no statistical difference (p =

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0.304). Conclusions: 1) There was a statistically significant difference of cognitive impairment prevalence between chemotherapy patients and non-chemotherapy control groups. 2) Among chemotherapy patients participated in baseline cognitive assessment, there was a statistically significant difference in cognitive impairment prevalence between pre- and post-chemotherapy assessment. 3) Among chemotherapy patients, there was a statistically significant difference in cognitive impairment prevalence between pre-perimenopausal patients and post-perimenopausal patients. 4) Among chemotherapy patients, there was a statistically significant difference in cognitive impairment prevalence between lower educated patients and higher educated patients. 5) Among TP regimen chemotherapy patients, there was no statistically significant difference in cognitive impairment prevalence between ovarian cancer patients and cervical cancer patients.

## Keywords

Gynecologic Cancer, Chemotherapy, Cognitive Impairment, Chemobrain

# 妇科癌症患者化疗后与认知功能障碍相关的研究

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## 摘要

目的: 1) 分析妇科癌症患者化疗后的认知功能状态。2) 分析化疗后认知功能障碍差异程度的相关因素。方法: 2009年至2011年, 妇科病房53名妇科癌症患者(Group A)入选本研究, 年龄为18岁至66岁, 其中患宫颈癌22例, 卵巢癌24例, 及其他妇科癌症7例。其中接受TP方案辅助化疗47例, 接受其他方案化疗6例。化疗病人分组, 根据他们的年龄(pre-perimenopausal <45岁和post-perimenopausal期 ≥45岁), 教育水平(低教育不到9年的教育和高等教育超过9年的教育), 类型的癌症(宫颈癌、卵巢癌、其他癌症), 类型的化疗方案(TP方案, 其他方案)。对照组分为两组, 非化学疗法的患者(B组)和健康对照组(C组)。根据患者的化疗情况分成5个研究组, 对照组分为2组。采用2个主观问卷调查( Everyday Memory Questionnaires及CAMDEX)和1个客观问题测试(Random Number Test), 根据问题答案对错计分, 判断受试对象的认知功能受损情况。问题测试在患者未接受任何治疗前(T1)和患者接受两次或者以上化疗疗程后3~4周后(T2)进行测试。患者的测试结果与对照组进行比较。结果: 1) 资料显示化疗患者比非化疗患者和健康对照组出现更多的认知问题。2) 在化疗前后自身对照研究中发现, 化疗后认知功能障碍与化疗前的有统计学差异( $p = 0.039$ )。3) 妇科癌症患者化疗后认知功能障碍, 在围绝经前组和围绝经后组间, 有统计学差异( $p = 0.031$ )。4) 妇科癌症患者化疗后认知功能障碍, 在文化程度高组和文化程度低组间, 有统计学差异( $p = 0.010$ )。5) 妇科癌症患者化疗后认知功能障碍, 在宫颈癌组和卵巢癌组间, 没有统计学差异( $p = 0.304$ )。结论: 1) 妇科癌症患者化疗后认知功能障碍与健康人组、非化疗病人组有统计学差异。2) 在化疗前后自身对照研究中发现, 化疗后患者认知功能障碍与化疗前的有统计学差异。3) 妇科癌症患者化疗后认知功能障碍, 在围绝经前组和围绝经后组间有统计学差异。4) 妇科癌症患者化疗后认知功能障碍, 在文化程度高组和文化程度低组间有统计学差异。5) 妇科癌症患者TP方案化疗后认知功能障碍, 在宫颈癌组和卵巢癌组间没有统计学差异。

## 关键词

妇科癌症, 化疗, 认知功能障碍, 化疗脑

## 1. 引言

癌症患者化疗后生存率一直在稳步提高, 妇科肿瘤患者也不例外。预计到 2020 年, 全球将有 7000 万癌症幸存者。随癌症存活生存率不断的上升, 医生正面临着新的问题——如何研究和治疗化疗引起的副作用[1]-[3]。有些化疗引起的副作用已经了解, 如免疫抑制, 骨髓抑制, 胃肠道不适, 不孕, 脱发等, 但对化疗引起认知功能障碍的机制认识不多[3] [4]。如果一个肿瘤患者, 化疗后成了一个痴呆病人, 实为医疗的悲剧。为了避免化疗后严重认知功能障碍的发生, 研究这种副作用出现的规律, 以及制定临床治疗方法显得非常迫切了。

在 1974 年, “化疗引起认知功能障碍”的现象首次被发现, 但直到 20 世纪 90 年代末, 医生和研究人员才确定化疗与认知功能障碍上的联系。这种认知功能障碍往往出现在化疗后, 也称为“化疗脑 chemobrain”, 这种副反应包括记忆力减退、注意力不集中、思考迟钝、以及其他微小认知缺陷的症状[5]-[8]。化疗作为辅助治疗, 使癌症患者生存率的上升, 导致化疗后认知功能障碍的病例明显增加。在这种情况下, 即使是认知功能损害轻微, 但患者持续的认知障碍会对患者以及家庭成员的生活质量带来相当大的负面影响。这种问题对于那些拥有专业和社会地位的病人来说, 更具危害性。因为注意力的缺乏或记忆丧失, 严重影响他们从事日常工作和担负社会责任[9]-[12]。另一方面, 这些损害影响了化疗病人选择相应治疗的判断力, 例如: 病人执意拒绝好的治疗方案, 却偏执地尝试有害的治疗方案, 造成治疗上的恶性循环, 使病情越来越严重, 终有一日病入膏肓[13] [14]。

为了增加对化疗与认知功能障碍之间关系的了解, 本研究分析妇科癌症病人化疗后, 认知功能的改变, 以及这种改变与各种因素的关系, 了解妇科癌症患者化疗脑发生的规律。使医务人员能更精确地拟定早期诊断该病标准、及作出的治疗决策、在化疗和生活质量二者之间得到更好的权衡。

## 2. 研究目的

分析妇科癌症患者化疗后的认知功能状态; 分析化疗后认知功能障碍差异程度的相关因素。

## 3. 资料和方法

2009 年至 2014 年, 妇科病房 63 名妇科癌症患者(Group A)入选本研究, 年龄为 18 岁至 66 岁, 其中患宫颈癌 41 例, 卵巢癌 22 例, 及其他妇科癌症 7 例。其中接受 TP 方案辅助化疗 57 例, 接受其他方案化疗 6 例。

根据患者的化疗情况; 年龄(围绝经前 45 岁以下, 围绝经后 45 岁以上); 文化程度(无高等教育——高中以下; 高等教育——高中以上); 癌症类型(宫颈癌, 卵巢癌和其他妇科癌症); 化疗方案类型(TP 方案, 非 TP 方案)分成 5 个研究组。对照组分为 2 组, 非化疗患者对照组(Group B)和健康对照组(Group C)。A 和 B 组无既往癌症或其他重大疾病史, 未接受激素治疗和脑部放射治疗史。C 组无任何重大疾病史。其他入选标准为: 年龄 18 至 70 岁, 至少有 6 年的正规教育。患神经或精神疾病者, 使用精神药物者, 有吸毒或酗酒的历史是从收集研究数据之前排除。

采用 2 个主观问卷调查( Everyday Memory Questionnaires 及 CAMDEX, 见附录)和 1 个客观问题测试(Random Number Test), 根据问题答案对错计分, 判断受试对象的认知功能受损情况。问题测试在患者未

接受任何治疗前(T1)和患者接受两次或者以上化疗疗程后 3~4 周后(T2)进行测试。患者的测试结果与对照组进行比较[15]-[17]。

#### 4. 讨论

1) 资料显示化疗患者比非化疗患者和健康对照组出现更多的认知问题, 主要存在于记忆的活动, 追溯和空间记忆这些方面[18] [19]。在需要有注意力、集中力和工作记忆的正常运行的客观测试中, 化疗患者的水平明显低于对照组。主观主诉和客观的测试之间相关。在至少 2 个测试使用  $SD = 1.5$  作为切断点, 或在至少 1 个测试中使用  $SD = 2$  作为切断点, 结果显示在 26.42%接受化疗治疗的患者表现出认知功能障碍, 而非化疗患者仅有 8.00%和健康对照组仅有 5.45%表现出认知功能障碍[20]。

2) 在化疗前后自身对照研究中发现, 有 33.33%接受化疗后的患者表现出认知功能障碍, 而化疗前的患者并未表现出认知功能障碍。化疗后认知功能障碍与化疗前的有统计学差异 ( $p = 0.039$ )。

3) 妇科癌症患者化疗后认知功能障碍, 有 37.93%围绝经后患者表现出认知功能障碍, 而围绝经前患者仅有 12.50%表现出认知功能障碍。在围绝经前组和围绝经后组间, 有统计学差异( $p = 0.031$ )。

4) 妇科癌症患者化疗后认知功能障碍, 有 42.31%无高等教育患者表现出认知功能障碍, 而高等教育患者仅有 11.11%表现出认知功能障碍。在文化程度高组和文化程度低组间, 有统计学差异( $p = 0.010$ )。

5) 妇科癌症患者化疗后认知功能障碍, 有 33.33%卵巢癌患者表现出认知功能障碍, 19.05%宫颈癌患者有表现出认知功能障碍。在宫颈癌组和卵巢癌组间, 没有统计学差异( $p = 0.304$ )。

#### 5. 结论

- 1) 妇科癌症患者化疗后认知功能障碍与健康人组、非化疗病人组有统计学差异。
- 2) 在化疗前后自身对照研究中发现, 化疗后患者认知功能障碍与化疗前的有统计学差异。
- 3) 妇科癌症患者化疗后认知功能障碍, 在围绝经前组和围绝经后组间有统计学差异。
- 4) 妇科癌症患者化疗后认知功能障碍, 在文化程度高组和文化程度低组间有统计学差异。
- 5) 妇科癌症患者 TP 方案化疗后认知功能障碍, 在宫颈癌组和卵巢癌组间没有统计学差异。

#### 参考文献 (References)

- [1] Minisini, A., Atalay, G. *et al.* (2004) What Is the Effect of Systemic Anticancer Treatment on Cognitive Function? *Lancet Oncology*, **5**, 273-282. [http://dx.doi.org/10.1016/S1470-2045\(04\)01465-2](http://dx.doi.org/10.1016/S1470-2045(04)01465-2)
- [2] Luo, L. and Craik, F.I. (2008) Aging and Memory: A Cognitive Approach. *Canadian Journal of Psychiatry*, **53**, 346-353.
- [3] Hannon, B. and Daneman, M. (2009) Age-Related Changes in Reading Comprehension: An Individual-Differences Perspective. *Experimental Aging Research*, **35**, 432-456. <http://dx.doi.org/10.1080/03610730903175808>
- [4] (2010) Hyperintensities. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, **19**, 1-17.
- [5] Ahles, T.A., Saykin, A.J., *et al.* (2002) Neuropsychologic Impact of Standard-Dose Systemic Chemotherapy in Long-Term Survivors of Breast Cancer and Lymphoma. *Journal of Clinical Oncology*, 485-493. <http://dx.doi.org/10.1200/JCO.20.2.485>
- [6] Poppelreuter, R.C., Mannes, A.J., Clark, U.S. and Bennett, G.J. (2004) Cognitive Dysfunction and Subjective Complaints of Cancer Patients: A Cross-Sectional Study in a Cancer Rehabilitation Centre. *European Journal of Cancer*, **40**, 43-49. <http://dx.doi.org/10.1016/j.ejca.2003.08.001>
- [7] Cimprich, B., So, H. *et al.* (2005) Pre-Treatment Factors Related to Cognitive Functioning in Women Newly Diagnosed with Breast Cancer. *Psychooncology*, **14**, 70-78. <http://dx.doi.org/10.1002/pon.821>
- [8] Tangpong, J., Cole, M.P., Sultana, R., *et al.* (2007) Adriamycin-Mediated Nitration of Manganese Superoxide Dismutase in the Central Nervous System: Insight into the Mechanism of Chemobrain. *Journal of Neurochemistry*, **100**, 191-201. <http://dx.doi.org/10.1111/j.1471-4159.2006.04179.x>

- [9] Weiss, B. (2008) Chemobrain: A Translational Challenge for Neurotoxicology. *Neurotoxicology*, **29**, 891-898. <http://dx.doi.org/10.1016/j.neuro.2008.03.009>
- [10] Konat, G.W., Kraszpulski, M., James, I., Zhang, H.T. and Abraham, J. (2008) Cognitive Dysfunction Induced by Chronic Administration of Common Cancer Chemotherapeutics in Rats. *Metabolic Brain Disease*, **23**, 325-333. <http://dx.doi.org/10.1007/s11011-008-9100-y>
- [11] Dietrich, J., Han, R.L., Yang, Y., Mayer-Prösche, M. and Noble, M. (2006) CNS Progenitor Cells and Oligodendrocytes Are Targets of Chemotherapeutic Agents *in Vitro* and *in Vivo*. *Journal of Biology*, **5**, 22. <http://dx.doi.org/10.1186/jbiol50>
- [12] Han, R.L., Yang, Y.M., Dietrich, J., Luebke, A., Mayer-Pröschel, M. and Noble, M. (2008) Systemic 5-Fluorouracil Treatment Causes a Syndrome of Delayed Myelin Destruction in the Central Nervous System. *Journal of Biology*, **7**, 12. <http://dx.doi.org/10.1186/jbiol69>
- [13] Tannock, I., Winocur, G., *et al.* (2006) The Effects of the Anti-Cancer Drugs, MTX and 5-FU on Cognitive Function in Mice. *Pharmacology Biochemistry and Behavior*, **85**, 66-75. <http://dx.doi.org/10.1016/j.pbb.2006.07.010>
- [14] Inagaki, M., Yoshikawa, E., Matsuoka, Y., *et al.* (2007) Smaller Regional Volumes of Brain Gray and White Matter Demonstrated in Breast Cancer Survivors Exposed to Adjuvant Chemotherapy. *Cancer*, **109**, 146-156. <http://dx.doi.org/10.1002/cncr.22368>
- [15] Silverman, D.H., Dy, C.J., Castellon, S.A., *et al.* (2007) Altered Frontocortical, Cerebellar, and Basal Ganglia Activity in Adjuvant-Treated Breast Cancer Survivors 5-10 Years after Chemotherapy. *Breast Cancer Research and Treatment*, **103**, 303-311. <http://dx.doi.org/10.1007/s10549-006-9380-z>
- [16] Mock, V., Atkinson, A., *et al.* (2000) NCCN Practice Guidelines for Cancer-Related Fatigue. *Oncology (Huntingt)*, **14**, 115-161.
- [17] Jenkins, V., Shilling, V., *et al.* (2006) A 3-Year Prospective Study of the Effects of Adjuvant Treatments on Cognition in Women with Early Stage Breast Cancer. *British Journal of Cancer*, **94**, 828-834. <http://dx.doi.org/10.1038/sj.bjc.6603029>
- [18] Hermelink, K. (2007) Cognitive Function during Neoadjuvant Chemotherapy for Breast Cancer: Results of a Prospective, Multicenter, Longitudinal Study. *Cancer*, **109**, 1905-1913.
- [19] Bender, C.M., Sereika, S.M., *et al.* (2006) Cognitive Impairment Associated with Adjuvant Therapy in Breast Cancer. *Psycho-Oncology*, **15**, 422-430. <http://dx.doi.org/10.1002/pon.964>
- [20] Wefel, J.S., Lenzi, R., *et al.* (2004) Chemobrain in Breast Carcinoma? A Prologue. *Cancer*, **101**, 46. <http://dx.doi.org/10.1002/cncr.20393>

## 附录

English Version Questionnaires

### PART A

CAMDEX (Yes = 1, No = 0)

- 1) Do you have any difficulty with your memory?
- 2) Do you forget where you have left things more than you used to?
- 3) Do you forget the names of close friends and relatives?
- 4) Have you been in your town and neighbourhood and forgotten your way?

### PART B

The Everyday Memory Questionnaire (EMQ)

The 'Everyday Memory Questionnaire' asks 27 questions about common memory lapses. Please rate the frequency with which you yourself make each lapse using the scale 1-9.

Place the score that represents how often you have experienced such a lapse on the line next to the question. Please rate all 27 common lapses.

Scale:

- 1 = Not at all in the last six months
- 2 = About once in the last six months
- 3 = More than once in the last six months
- 4 = About once a month
- 5 = More than once a month, but less than once a week
- 6 = About once a week
- 7 = More than once a week, but less than once a day
- 8 = About once a day
- 9 = More than once a day

1. Forgetting where you have put something. Losing things around your house
2. Failing to recognize places that you are told you have often been to before
3. Finding a television story difficult to follow
4. Not remembering a change in your daily routine, such as a change in the place where something is kept, or a change in the time something happens. Following your old routine by mistake
5. Having to go back & check whether you've done something that you meant to do
6. Forgetting when something happened; for example, forgetting whether something had happened yesterday or last week
7. Completely forgetting to take things with you, or leaving things behind, or having to go back and fetch them
8. Forgetting that you were told something yesterday or a few days ago, and maybe having to be reminded about



it

9. Starting to read something (a book or, a newspaper or magazine article) without realizing you have already read it before
10. Letting yourself ramble on to speak about unimportant or irrelevant things
11. Failing to recognize, by sight, close relatives or friends that you meet frequently
12. Having difficulty picking up a new skill. For example, having difficulty in learning a new game or in working some new gadget after you have practised once or twice
13. Finding that a word is 'on the tip of your tongue'. You know it, but cannot quite find the word
14. Completely forgetting to do things you said you would do, and planned to do
15. Forgetting important details of what you did or what happened to you yesterday
16. When talking to someone, forgetting what you have just said.
17. When reading a newspaper or magazine being unable to follow the thread of a story; losing track of what it is about
18. Forgetting to tell someone something important. Perhaps forgetting to pass on a message or remind someone of something
19. Forgetting important details about yourself, e.g. your birthday or where you live
20. Getting the details of what someone had told you mixed up and confused
21. Telling someone a story or joke you have told them once already
22. Forgetting details of thing you do regularly, whether at home or at work. For example, forgetting details of what to do, or at what time to do it
23. Finding that faces of famous people, seen on television or in photographs, look unfamiliar
24. Forgetting where things are normally kept or looking for them in wrong place
25. (a) Getting lost or turning in the wrong direction on a journey, a walk, or in a building where you have OFTEN been before  
(b) Getting lost or turning in the wrong direction on a journey, a walk, or in a building where you have ONLY BEEN ONCE OR TWICE BEFORE
26. Doing some routine thing twice by mistake. For example, going to brush/comb your hair, or putting two lots of tea in the pot, when have just done so
27. Repeating to someone what you have just told them or asking them the same question twice