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# Evaluation of DNA Versus Collagen Perception in Scientific Articles Examining Cancer and Chemotherapy: Implication for Collagen Based Approaches

Kanser Kemoterapisini İnceleyen Bilimsel Makalelerde DNA'ya Karşı Kolajen Algısının Değerlendirilmesi: Kollajen Temelli Yaklaşımlar için Çıkarım

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***ABSTRACT***

***Objective:*** *Although cancer chemotherapy has been used for more than seventy years, its definitive mechanism of action is not known. Many studies indicate that beyond DNA the collagen connective tissue matrix is also affected. This database analysis aims to determine the extent of DNA versus collagen perception in scientific papers indexed under PubMed.*

***Material and Method:*** *The PubMed database scanned on September, 15, 2021 using following keywords and combinations; "cancer", "cancer chemotherapy", "cancer chemotherapy AND damage", "chemotherapy AND mechanism AND damage", "chemotherapy AND clinical" as nominator. The number of items found for each search was proportioned in terms "DNA versus collagen" and the ratio was accepted as the perception shift coefficient.*

***Results:*** *Tested with the p1-p2 analysis to calculate the difference between the two proportions in both search items. Based on the main rule under the assumption that "all cells have DNA and all cells live in the collagen matrix". In the p1-p2 analysis of the data, a significant ($p < 0.001$) difference was obtained for all dichotomy scans.*

***Conclusion:*** *This data analysis supports the argument that both cancer and chemotherapy perception is DNA-based rather than collagen, since the synthesis and degradation process of very slow; it is not possible to observe it in short term studies. Chemotherapy should be further analyzed by this manner in purpose of collagen matrix.*

***ÖZET***

***Amaç:*** *Kemoterapi yetmiş yıldan fazla bir süredir kullanılmasına rağmen, kesin etki mekanizması bilinmemektedir. Birçok çalışma, DNA'nın ötesinde kolajen bağ dokusu matrisinin de etkilendiğini göstermektedir. Bu veri tabanı analizi, PubMed altında indekslenen bilimsel makalelerde DNA'ya karşı kolajen algısının kapsamını belirlemeyi amaçlar.*

***Gereç ve Yöntem:*** *Aşağıdaki anahtar kelimeler ve kombinasyonlar kullanılarak 15 Eylül 2021'de taranan PubMed veri tabanı; Aday olarak "kanser", "kanser kemoterapisi", "kanser kemoterapisi VE hasarı", "kemoterapi VE mekanizması VE hasarı", "kemoterapi VE klinik". Her arama için bulunan öğe sayısı "DNA'ya karşı kolajen" ve oran algı kayması katsayısı olarak kabul edildi.*

***Bulgular:*** *Her iki arama öğesindeki iki oran arasındaki farkı hesaplamak için p1-p2 analiziyle test edildi. "Bütün hücrelerin DNA'sı vardır ve tüm hücreler kolajen matriks içinde yaşar" varsayımı altındaki ana kurala dayanmaktadır. Verilerin p1-p2 analizinde tüm dikotomi taramaları için anlamlı ($p < 0,001$) fark elde edildi.*

***Sonuç:*** *Bu veri analizi, hem kanser hem de kemoterapi algısının, sentez ve degradasyon süreci çok yavaş olduğu için kolajenden ziyade DNA bazlı olduğu argümanını desteklemektedir; kısa süreli çalışmalarda bunu gözlemlemek mümkün değildir. Kemoterapi, kolajen matriks amacıyla bu şekilde daha fazla analiz edilmelidir.*

***Keywords:***
*Chemotherapy*
*DNA*
*Collagen*
*Dichotomy*

***Anahtar Kelimeler:***
*Kemoterapi*
*DNA*
*Kolajen*
*Dikotomi*

## INTRODUCTION

Cancer is a global health problem increasing with industrialization and the second cause of death in developed countries (1-3). Although archaeological studies indicate that cancer can be observed also in ancient times, it is generally accepted that the incidence of the disease is increasing rapidly today (4, 5).

Despite the disease burden and economic cost caused by cancer, studies conducted to understand the etiopathogenesis of the disease is behind the expected success, indicating the possibility of a biased error rather than a random one. For instance, etiopathological explanations of diseases in medicine generally accepted a cell-centered approach. According to this idea, cancer is considered as uncontrolled cell proliferation, focusing on the cell itself (6). In the middle of the last century, after the approvement that genetic information is encoded in DNA, this idea also led to the acceptance that cell division is controlled by DNA (7,8) This perspective evoked an influence that the biological effects of both radiotherapy and chemotherapy are directly related to the damage or changes in DNA.

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An important invention in a field could diffuse to the other areas and influence in a similar manner, which is called as Zeitgeist effect (9). The interpretation of cancer through DNA affected the proposed mechanism of action of chemotherapeutic drugs in the same manner. The development of chemotherapeutic drugs emerged in the second half of the twentieth century in demand for relevant treatment strategies elevated, as the incidence of leukemia and lymphomas rise. This period starts with the use of alkylating agents, followed by many candidate chemicals which have been rapidly tested in cell culture (10, 11). In this period, DNA attracted all the scientific attention as a miracle molecule, which leads to the interpretation of the effects of chemotherapeutic agents through interference with DNA synthesis (12). In addition, DNA has a relatively simple molecular structure which facilitates studies utilizing DNA-based research.

However, unlike the cell culture in the tissue cells are located in the connective tissues composed of collagen. Indeed, collagen is the main component of connective tissue and establishes a class of more than 30 divers molecules, the largest part of body structural proteins. Apart from being difficult to investigate since collagen shows a very slow production-destruction cycle in the organism, its effect on the emergence of the disease has not been adequately studied (13-15).

The DNA-based approach argues that genetic information as the cause of cancer for all that genetic cancers or mutations leading to malignancies are very limited, accounts for only a very small proportion of the cases (16,17). The genetic perspective focuses on the "clonogenic cell" idea and categorizes the disease as a genetic coding error. On the other hand, cancer disease is still under interpretation, even today, due to both its etiopathogenesis and therapeutic modalities. The changes that lead to malignancy could also be explained as a connective tissue disorder. However, it is not easy to determine how large an alternative explication is covered by the mainstream explanation. For this purpose, one can analyze the entire database by using keywords. The basic logic of this method is that the concepts studied are in the same system, but not directly related to each other. The observed and the detected values in any data analysis are the sums of the actual, coincidental and false results (bias). Although everything can affect the other one in living systems, choosing the right keywords will narrow the possibility of error. This study is a database analysis performed to determine the bias of "DNA versus collagen" perception on the basis of cancer and chemotherapy.

## MATERIAL AND METHOD

The database of The United States National Library of Medicine encodes scientific publications under keywords (Medical Subject Headings, MeSH) defined as medical titles (18). This database structure gives a numerical value for any MeSH if used as a nominator. When a second MeSH keyword for the dichotomy is added to the search (fuzzification), the numerical values obtained indicate the association of the nominator with the second concept. The ratio of the numerical result given by the same nominator with the two sub-concepts obtained by dichotomy will determine the severity of the research direction (19).

In order to evaluate the perception of cancer and chemotherapy retrospectively, the PubMed database was searching on September, 15, 2021 using the medical keywords "cancer", "cancer chemotherapy", "cancer chemotherapy AND damage", "chemotherapy AND mechanism AND damage", "chemotherapy AND clinical" as nominator. In the second phase, the association of these key terms were searched by creating a dichotomy by adding "DNA" or "collagen" MeSH for each item. A separate search was carried out by changing the order of the words used in order to test whether the "AND" logic shows a sort of relationship with the words on the search results. It was observed that the obtained article order and numerical values completely overlapped, thus it was confirmed that the PubMed database was not affected by the keyword ranking.

The sizes of the numerical numbers obtained with keywords were accepted as the "correlation value". No exclusion criteria were used in screening. Since the database contains a large number of articles, it was not possible to evaluate all the results, and samples were selected by considering the random numbers table. The accessed results with each MeSH or combination were randomly reviewed for 50 articles and the search was expanded by increasing the number of words that occur together the possibility of biases was refused. The numbers obtained by each nominator either with DNA or collagen subtitles were divided to the each other; obtained results were called the perception shift ratio.

### Statistics

When interpreting a confidence interval that compares two population proportions, one should always be sure to use the words of the problem and to phrase the interpretation in terms of how much larger (or smaller) the first proportion is compared to the second one. This procedure is valid because both samples were taken randomly and independently. In this way it is common to compare two independent groups with respect to the presence or absence of a dichotomous characteristic or attribute, when the outcome is dichotomous, the analysis involves comparing the proportions of successes between the two groups.

There are several ways of comparing proportions in two independent groups. One can compute a proportion difference, which is computed by taking the difference in proportions between comparison groups and is similar to the estimate of the difference in means for a continuous outcome. Generally, the reference group (e.g. chemotherapy) is considered in the denominator of the ratio. The dichotomy ratio is a good measure of the strength of an effect (ie. DNA versus collagen) and therefore provides an indication for a reason attributed. When the outcome of interest is relatively uncommon (e.g., <10%), a dichotomy ratio has a good predictive value, confidence interval estimates for the dichotomous difference.

In this study, the results obtained were tested with the p1-p2 analysis to calculate the difference between the two proportions in both search items. Based on the main rule under the assumption that "all cells have DNA and all cells live in the collagen matrix" H0 hypothesis has

been created for significance; H0: p1-p2 = 0 and H1: p1-p2 ≠ 0 as exclusion criteria. The numerical results were statistically analyzed for the fact of H0> H1 condition, p <0.01 was considered significant.

**RESULTS**

Results are shown in the table and figures. In the articles containing "cancer", "cancer chemotherapy", "chemotherapy AND damage," chemotherapy AND mechanism AND damage, "chemotherapy AND clinical", the association with DNA was found to be higher than with collagen. While 396,459 of the 4,430,969 articles with the word cancer in them was DNA passed, collagen was passed together in 29,217. When the screening was done with the keywords "cancer chemotherapy" as nominator, 315,921 results were obtained, whereas 68,174 articles were obtained when "DNA" was used for dichotomy, 4,968 for "collagen" were obtained respectively. DNA dichotomy rate was found 3.88 to 62.51 times higher in all search MeSHs compared to collagen in the database (20, 21).

In the p1-p2 analysis of the data, a significant (p <0.001) difference was obtained for all dichotomy scans. Thus, the H0 hypothesis was excluded and the H1 hypothesis was confirmed, it has been shown in the PubMed database for search items "cancer", "cancer chemotherapy", "chemotherapy AND damage," chemotherapy AND mechanism AND damage, " chemotherapy AND clinical", have a statistically significant association with DNA than collagen.

**DISCUSSION**

Search and analysis of classified and stored data is called data mining (22, 23). In practical view, (i) the data must be stored in an integral accessible electronic concept. (ii) The searched elements should be coded with a characteristic term (Medical Subject Headings, MeSH) that will not cause confusion (iii) The database should be open to the "AND/OR" proposition. United States National Library of Medicine consist a data base in which the scientific publications are encoded with keywords since its establishment (24, 25).

The development of computers and the communication technology enable to search and handle big databases. Since the PubMed database is big enough, it can be explored how much a concept had been associated with other related one (dichotomy) if valid keywords are used (eg.DNA vs. collagen). This database does not contain duplications and therefore allow objective data analysis. In this way scientific articles could be searched with two or more MeSH keywords. Searching this specific

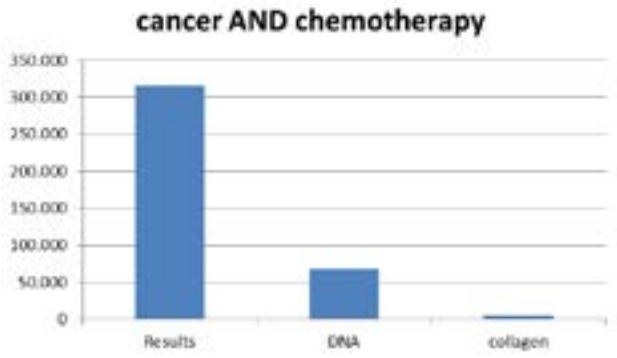


**Figure 1:** Results for "cancer AND chemotherapy '' MeSH, following bars demonstrate DNA versus collagen dichotomy.

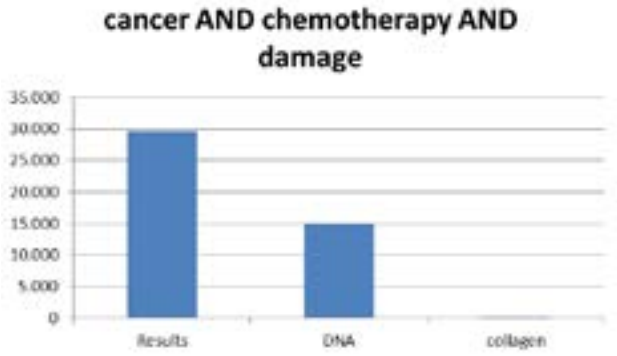


**Figure 2:** Results for "cancer AND chemotherapy AND damage '' MeSH, following bars demonstrate DNA versus collagen dichotomy.


**Figure 3:** Results for "chemotherapy AND mechanism AND damage '' MeSH, following bars demonstrate DNA versus collagen dichotomy.

**Table :** Results and statistical analysis obtained by each PubMed database search according to nominator and dichotomous MeSH words.

| KEYWORDS | Results | DNA | Collagen | DNA/Collagen | Z value | P value |
|---|---|---|---|---|---|---|
| **cancer** | 4430969 | 396459 | 29217 | 13.57 | 25415.454. | < .00001 |
| **cancer AND chemotherapy** | 315921 | 68174 | 4968 | 13.73 | 2949.4758. | < .00001 |
| **cancer AND chemotherapy AND damage** | 29673 | 14940 | 239 | 62.51 | 419.5045. | < .00001 |
| **chemotherapy AND mechanism AND damage** | 23744 | 6881 | 536 | 12.84 | 617.8065. | < .00001 |
| **chemotherapy** | 3580290 | 127482 | 32821 | 3.88 | 62451.289. | < .00001 |
| **chemotherapy AND clinical** | 1326524 | 45989 | 10798 | 4.26 | 38463.3885. | < .00001 |

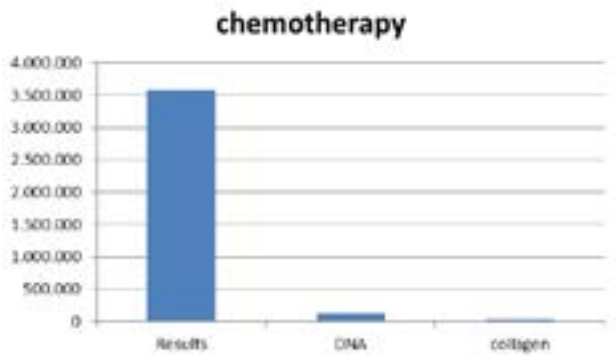


**Figure 4:** Results for ‘‘chemotherapy ‘’ MeSH, following bars demonstrate DNA versus collagen dichotomy.

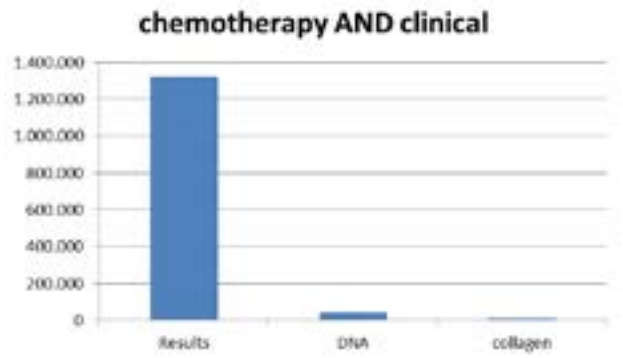


**Figure 5:** Results for ‘‘chemotherapy AND clinical ‘’ MeSH, following bars demonstrate DNA versus collagen dichotomy.

nominator reference group along with other MeSH item will provide dichotomy, which is indicative for assuming relationships; i.e. the keywords “cancer and DNA” or “cancer and collagen”.

The dichotomy subjects in this study are DNA and collagen, the reference groups used before dichotomy is completely different, and so it is not possible to interpret the results with bias. On the other hand, the vastness of the database creates homogenization within itself, even if there is a random bias, its effect could be excluded due to homogenization. It can be also argued that the journals published in different fields may lead to biases but selecting the keywords from the MeSH scope limits this possibility.

The results of this database analysis support that even cancer or chemotherapy perception is DNA-referred. However, most tumors occur with tissue changes over several years (26). In addition, it should be noted that since genes that are thought to be associated with cancer are actually found in all cells, which also operate completely different functions.

Chemotherapy is one of the main therapeutic approaches in cancer treatment, which was developed in the second half of the last century. The mechanisms of action of chemical substances used for chemotherapy have been attributed to DNA but have not been studied in detail. Indeed, most of them are not selective and interacts with mechanisms other than DNA, which make sense when the side effect profiles take into consideration. Most antibiotics can disrupt the extracellular matrix (27), i.e., drugs like docetaxel that affect the formation of mitotic spindles, can interact directly or indirectly with the inner and outer cytoskeleton (28).

On the other hand, studies to explore the effects of chemotherapy on connective tissue have limitations. Since the synthesis and degradation process of collagen is very slow, it is not possible to observe it in short-term studies. In addition, there is no known exact biochemical methodology to evaluate the degradation end-products of most collagen types, even in experimental systems (29,30). However, some studies in this area indicate that chemotherapeutics could interact with collagen (31). Cisplatin, which is used in many gastrointestinal cancer protocols, interferes with the synthesis process of collagen (32). Adriamycin, which is frequently used in breast cancer and soft tissue sarcomas, causes modifications in collagen structure (33, 34). Bleomycin, an antibiotic chemotherapeutic agent commonly used in the treatment of testicular cancers, causes the alterations of the extracellular matrix (35). These data also indicate that the occurrence of cardiomyopathy, which is long-term and dose-limiting adverse effect of Adriamycin, can be explained by its interaction with the fibrous skeleton of the heart. Similarly, bleomycin-induced lung fibrosis could be explicated through its relation with specific lung collagen structure (36).

## CONCLUSION

In conclusion, this data analysis supports the argument that both cancer and chemotherapy perception is DNA-based, but it could be also attributed to collagen, the main component of connective tissue. Although the data in the literature are very limited, it is clear that collagen and extracellular matrix constitutes a new and productive field for investigating the effects of chemotherapy. Future studies could be very beneficial if objected to connective tissue instead of a DNA-based perception.

**Conflict of interest:** No conflict of interest was declared by the authors

**Ethics:** The study does not require ethics committee approval. This study is an evaluation of statistical results in accordance with our own ideas. It is not in the category required for the ethics committee approval application. There is no such thing as any blood, saliva, violation of the rights of the patient, etc.

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