The European Research Journal 2023;9(1):22-28 Original Article

DOI: 10.18621/eurj.1053651 *Radiation Oncology*

Evaluation of DNA versus collagen perception in scientific articles examining cancer and radiation therapy: implication for collagen-based approaches

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ABSTRACT

Objectives: Although radiation therapy has been used for more than a hundred years, its definitive mechanism of action is not known. Many studies indicate that radiation induces free radicals which damage DNA. However, irradiation should also affect the collagen connective tissue matrix. This database analysis aims to determine the extent of DNA versus collagen perception in scientific papers.

Methods: Journals indexed in PubMed were searched on March 3, 2021, using the medical keywords "cancer", "radiation therapy", "radiation therapy AND damage," radiation therapy AND mechanism AND damage, "radiation therapy AND clinical". The number of items found for each search was proportioned in terms of "DNA versus collagen" and the ratio was accepted as the perception shift coefficient.

Results: Results were tested with the p-value 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.

Conclusions: This data analysis supports the argument that both cancer and radiation therapy 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. The effects of irradiation should be further analyzed in this manner for purpose of collagen matrix interaction.

Keywords: Radiation therapy, DNA, collagen, fuzzification

Radiation therapy is one of the main modalities in cancer treatment. Ionizing radiation had been used in the treatment of many diseases, even shortly after the discovery of its biological effects [1]. The first successful radiotherapy trials were performed in head and neck cancers, where surgical treatment was not possible, followed by other malignancies [2]. Based on the observations of the radiation tolerance of normal tissues, it was noticed that dividing the dose into fractions over time (fractionation) increased normal tissue tolerance, without a negative effect on tumor control, therefore, the concept of fractionated radiation therapy was emerged [3].

Although the general biological principles of radiation therapy had rapid progress, the mechanism of action continues to be a subject of debate even today.

Received: ***January 5, 2022;*** *Accepted:* ***April 27, 2022;*** *Published Online:* ***October 3, 2022***

How to cite this article: *Karaman Ş, Karaçay Ö, Dizdar Y. Evaluation of DNA versus collagen perception in scientific articles examining cancer and radiation therapy: implication for collagen based approaches. Eur Res J 2023;9(1):22-28. DOI: 10.18621/eurj.1053651*

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e-ISSN: 2149-3189

According to the radiobiological observations, the cells that divide faster have been affected than those that divide slowly; thus it has been generally accepted that the biological effect is related to the cell division rate [4, 5]. After the discovery that the genetic information is encoded in the DNA molecule, a consensus appeared that the control of cell division is related to DNA. This point of view led to the conclusion that the biological effects of radiation are directly related to DNA damage which is still valid today. According to this idea "radiation can cause single or double-strand breaks in DNA, resulting in fatal mutations or programmed cell death" [6].

However, in an intact organism, all cells are located in an extracellular matrix where the main component is collagen and the control of cell division is regulated by external stimuli. Although DNA encodes a complex synthesis process, it is structurally a simple molecule, that situation orientated the research toward DNA and facilitates DNA-based explanations for radiation effects. In contrast, the turnover of the collagen matrix is very slow and complex even to observe or explore. While cancer cells can be investigated under in vitro conditions, the collagen matrix production-destruction cycle is out of research scope due to its slow turnover and methodological limitations [7-9].

All these reasons have led to the establishment of a DNA-focused mainstream explanation of the biological mechanism of action for ionizing radiation. Thus the probable interaction of radiation with collagen seems to be overlooked. In contrast, it is not easy to determine how much an alternative second explanation overlaps the main explanation. One of the valid methods that can be applied for this purpose is the screening of associated medical subjects in this field and the testing of whether the difference between the matches is statistically significant, the approach is generally called fuzzification [10]. In this method, first, the main heading (nominator) is searched on the database and then their association (dichotomy) with the subheadings is researched. This approach produces numerical output for related subjects and they can be further analyzed.

Today, information technology enables access to large databases of peer-review scientific articles. The basic logic in this method is that the concepts studied are in the same system, but not directly related to each other. The result observed and the detected value in any data analysis is the sum of the actual, coincidental, and false results (bias). Although everything can be associated with another concept 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 based on cancer and radiation therapy research.

METHODS

The database of the United States National Library of Medicine encodes scientific publications with keywords Medical Subject Headings (MeSH) defined as medical titles [11]. This database structure gives a numerical value if any MeSH is used as a nominator. When a second MeSH keyword for 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 subconcepts obtained by dichotomy will determine the direction of research perception [12].

To evaluate the scientific perception of cancer retrospectively, the PubMed database was searched on March 3, 2021, using the medical keywords "cancer", "radiation therapy", "radiation therapy AND damage," radiation therapy AND mechanism AND damage, "radiation therapy AND clinical". In the second phase, the association of these key terms was searched by creating a dichotomy by adding "DNA" or "collagen" MeSH for each item. In order to test whether the "AND" logic shows a collocation relationship within the MeSH search results, a separate search was carried out by replacing the words used. 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 numerical 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 search MeSH or combinations were randomly re-

viewed with 50 articles and the possibility of biases was refused. Later, the search was expanded by increasing the number of words that occur together; herewith the bias that the results contain search words together due to a random error was excluded.

The results obtained by each search nominator either with its DNA or collagen subtitles were rated to each other; the number obtained was called the perception shift ratio. Although the database search found a narrower set of results with each different option (DNA versus collagen) added to the nominator, the value of the perception shift coefficient remained in favor of DNA versus collagen.

Statistical Analysis

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 ratio compared to the second one. This procedure is valid because both samples were taken randomly and independently. So 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. radiation therapy) 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 indicates 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 [13].

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" the 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 the H0 > H1 condition, $p < 0.01$ was considered significant. [14, 15].

SPSS was used in the calculations made during the study (to compare the effect of independent variables on dependent variables).

RESULTS

In the articles including "cancer", "radiation therapy", "radiation therapy AND damage," radiation therapy

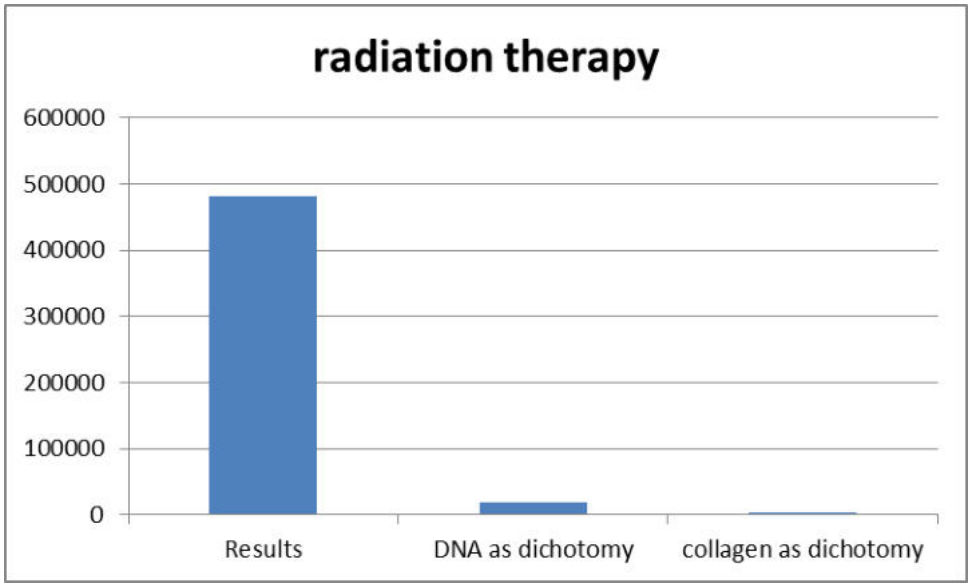

Fig. 1. Results for "radiation therapy" Medical Subject Headings, following bars demonstrate DNA versus collagen dichotomy.

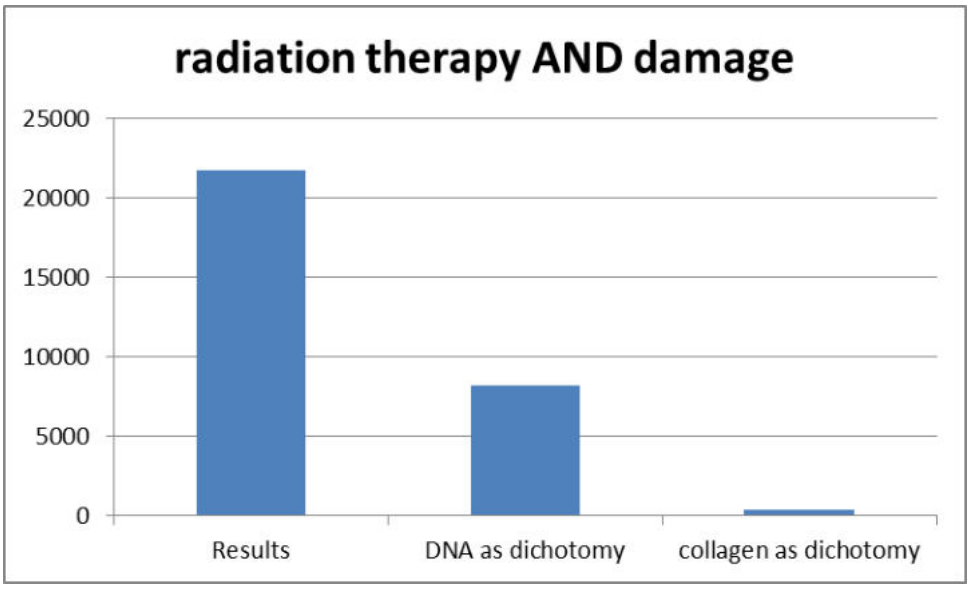

Fig. 2. Results for "radiation therapy AND damage" Medical Subject Headings, following bars demonstrate DNA versus collagen dichotomy.

AND mechanism AND damage, "radiation therapy AND clinical", the association with DNA was found higher than associating with collagen. Of a total of 4,569,302 articles with the MeSH cancer, 407,585 include DNA, whereas collagen was included in 30,087. If the search MeSH "radiation therapy" was used as nominator, 496,547 results were obtained, which resulted in 20487 articles when using "DNA"; and 2,846 using "collagen" for dichotomy respectively. According to these results dichotomy rate in the database favors DNA compared to collagen 7.2 to 30.4 times for all search MeSH items (Table 1). The detailed analyzes of the results in Table 1 are shown in Figs. 1, 2, 3 and 4.

In evaluating the significance of the difference between the groups compared in studies, the issue that is almost always taken into consideration is whether it is statistically significant. In other words, the p-value is less than 0.05. In our study, the *p* - value was statistically significant. However, since the p-value is affected by the sample size, the results were tested with the effect size factor to show that this significance was

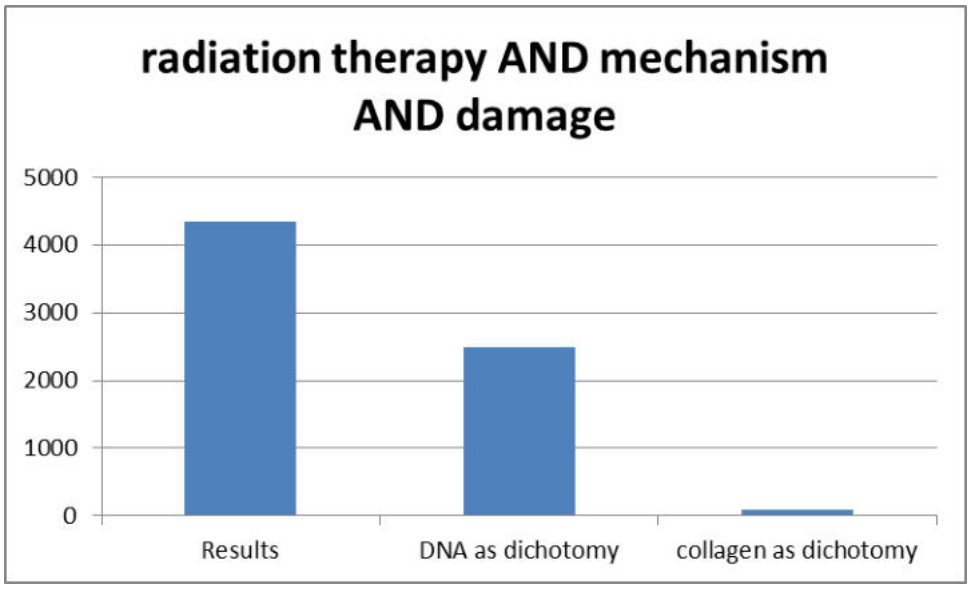

Fig. 3. Results for "radiation therapy AND mechanism AND damage" Medical Subject Headings, following bars demonstrate DNA versus collagen dichotomy.

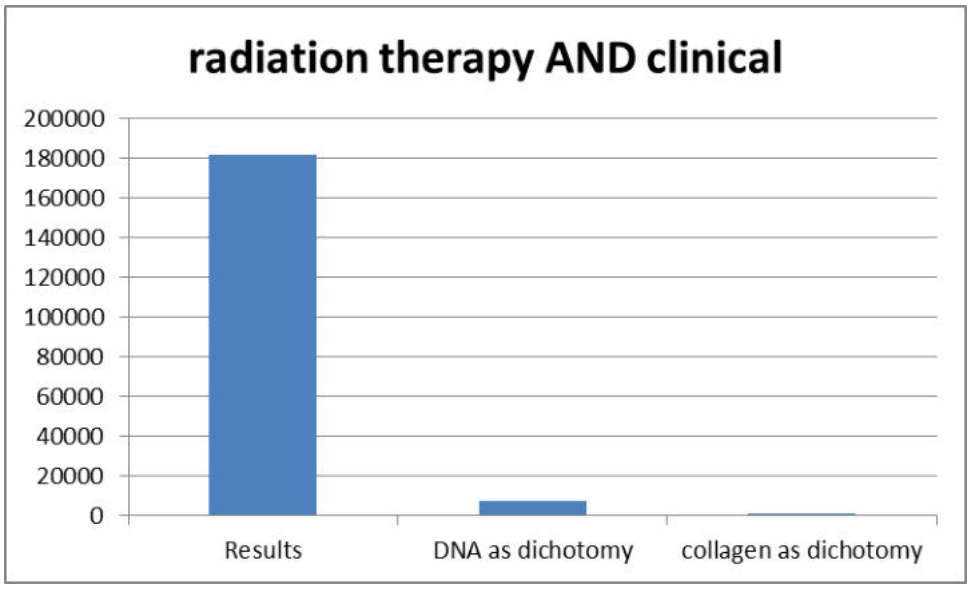

Fig. 4. Results for "radiation therapy AND clinical" Medical Subject Headings, following bars demonstrate DNA versus collagen dichotomy.

not accidental.

The effect size shows how much of the total variance in the dependent variable is explained by the independent variable or factor. The most widely used one in calculating the effect size is the calculation developed by Cohen (d). As a general recommendation, Cohen says that if the d value is less than 0.2, the effect size can be defined as weak, if 0.5 is medium, and if it is greater than 0.8, it can be defined as strong [16]. The data of the Cohen's d test, the results of which we tested, are given in Table 2.

When the effect size results were examined, it was confirmed that there were remarkable results greater than 0.8 and the p-value was not random.
Statistical evaluation of the data with p1-p2 analysis was found to be significantly different ($p < 0.001$) for all dichotomy results, thus ruling out the H0 hypothesis and confirming the H1 hypothesis. The results show that within the PubMed database the search terms "cancer", "radiation therapy", "radiation therapy AND damage," radiation therapy AND mechanism AND damage", and "radiation therapy AND clinical" have a very close association with DNA than associating them with collagen.

DISCUSSION

Today, information technology enables the search and analysis of large databases with relevant keywords. Based on this study, PubMed offers the opportunity to access millions of peer-review scientific articles online

Table 1. Output values and statistical analysis results obtained by each PubMed database search according to nominator and dichotomous Medical Subject Headings (MeSH) words.

Search MeSH	Results	DNA as dichotomy	Collagen as dichotomy	DNA / collagen	Z value	*p* value
Cancer	4,569,302	407,585	30,087	13.54	25448.476	**< 0.00001**
Radiation therapy	496,547	20,487	2,846	7.2	18760.6098	**< 0.00001**
Radiation therapy AND damage	22,660	8,645	410	21.1	463.0428	**< 0.00001**
Radiation therapy AND mechanism AND damage	4,627	2,676	88	30.4	143.5726	**< 0.00001**
Radiation therapy AND clinical	189,707	7,950	1,028	7.7	11366.6028	**< 0.00001**

Table 2. The effect size of the statistical analysis results of the values obtained according to the candidate and binary Medical Subject Headings words with each PubMed database search

Group 1: DNA Group 2: Collagen	Cohen's d	Effect-size r
Cancer	1.15	0.49
Radiation therapy	0.78	0.36
Radiation therapy AND damage	1.03	0.46
Radiation therapy AND mechanism AND damage	1	0.44
Radiation therapy AND clinical	0.85	0.39

[17, 18]. Since the PubMed database is very large, if valid keywords are plotted, it can be explored how much a concept had been associated with other related items (dichotomy). This database does not contain duplications; all journals within its scope feature peer-review and therefore allow objective data analysis.

The dichotomy subjects in this study are DNA and collagen, the reference groups used before the dichotomy are completely different, so it is not possible to interpret the results with bias. On the other hand, the fact that the database is very large, creates homogenization within itself. It can be argued that the journals published in different fields may also be the cause of bias, but selecting the keywords used in the search from the MeSH scope limits the bias possibility. One can use the p1-p2 hypothesis in statistical evaluation in the analysis of large databases. The PubMed, which covers knowledge of more than a century, supports the hypothesis that scientific opinion held DNA significantly more responsible than collagen in explaining cancer, radiation therapy, and its mechanism of action. The etiology of cancer is still unknown today. Cancer disease can be detected also in archaeological records [19]. However, it is generally accepted that cancer has increased in all countries of the world especially in the last decades [20-22]. Hundred years ago it was understood that the cell nucleus plays an ad hoc role in cell division, and it was proven in the second half of the last century that DNA encodes genetic information. This situation has attracted the attention through the genetic characteristics of diseases and put the microenvironment in which the cell is located to be ignored. All the environmental factors, which are claimed to play a role in cancer development, have been associated with DNA damage. This approach, which can also be called the Zeitgeist effect, lead to huge progress that enable DNA analysis with automatic devices in a short time and reinforced the shift of perception of cancer etiopathogenesis and treatment to the DNA-centric [23, 24]. However, even though the cell division is encoded in DNA, the stimulus that will initiate the division comes from the intercellular area, especially through extracellular matrix components, rather than DNA [25]. In contrast to DNA, the intercellular field is characterized by dynamics that cannot be easily investigated, and the slow turnovers do not allow observation.

Studies on the biological effects of radiation therapy on collagen are extremely limited. Although it has been known for a long period that radiation interacts with collagen, it has not been possible to test the effect in vivo. Even though early research indicated that radiation cause collagen damage, the Zeitgeist effect shifted the perception to DNA. Moreover, technical facilities limited the studies on interactions of radiation with the extracellular matrix, especially collagen [26, 27].

In contrast, current clinical experience confirms that radiation affects connective tissue (unlike DNA) in long term. Fibrosis occurring after radiation therapy is permanent even in conventional therapeutic doses; causing functional defects in the heart, bladder, or rectum [28-30]. Moreover, the lens, which is very sensitive to irradiation, is acellular and contains only cells in the boundary of the capsule, but loses its light transmittance even in very low doses [31].

CONCLUSION

This study confirmed that cancer, radiation therapy, damage, and mechanisms of action have been attrib-

uted to DNA significantly more than collagen, the main intercellular matrix component, in which the cell is located. Although the data in the literature are very limited, it is clear that collagen and extracellular matrix constitute a new and productive field for exploring the effects of radiation. Future studies could be very beneficial if objected to connective tissue instead of a DNA-based perception.

Authors' Contribution

Study Conception: ÖK; Study Design: ŞK; Supervision: ŞK; Funding: ŞK; Materials: YD; Data Collection and/or Processing: YD; Statistical Analysis and/or Data Interpretation: ÖK; Literature Review: ŞK; Manuscript Preparation: YD and Critical Review: ÖK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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