The 100 Most Cited Papers About Cancer Epigenetics

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Abstract

Introduction

Although bibliometric analyses have been performed in the past on cancer and genomics, little is known about the most frequently cited articles specifically related to cancer epigenetics. Therefore, the purpose of this study is to use citation count to identify those papers in the scientific literature that have made key contributions in the field of cancer epigenetics and identify key driving forces behind future investigations.

Materials and methods

The Thomas Reuters Web of Science services was queried for the years 1980-2018 without language restrictions. Articles were sorted in descending order of the number of times they were cited in the Web of Science database by other studies, and all titles and abstracts were screened to identify the research areas of the top 100 articles. The number of citations per year was calculated.

Results

We identified the 100 most-cited articles on cancer epigenetics, which collectively had been cited 147,083 times at the time of this writing. The top-cited article was cited 7,124 times, with an average of 375 citations per year since publication. In the period 1980-2018, the most prolific years were the years 2006 and 2010, producing nine articles, respectively. Twenty-eight unique journals contributed to the 100 articles, with the Nature journal contributing most of the articles (n=22). The most common country of article origin was the United States of America (n=78), followed by Germany (n=4), Switzerland (n=4), Japan (n=3), Spain (n=2), and United Kingdom (n=2).

Conclusions

In this study, the 100 most-cited articles in cancer epigenetics were examined, and the contributions from various authors, specialties, and countries were identified. Cancer epigenetics is a rapidly growing scientific field impacting translational research in cancer screening, diagnosis, classification, prognosis, and targeted treatments. Recognition of important historical contributions to this field may guide future investigations.

Categories: Genetics, Oncology, Other

Keywords: epigenetic, cancer, molecular biomarker, citation analysis, bibliometrics, DNA methylation

Introduction

In 1942, Conrad Hal Waddington was the first to use the Greek word "epigenesis", to describe how cells differentiated, and thus epigenetics was coined to mean "the causal interactions between genes and their products which bring the phenotype into being" [1]. But it was not until the 1970s when the contemporary definition emerged as "a heritable change in gene expression that occurred without a change in the DNA sequence" [2]. Broadly speaking, as it applies to modern cancer biology, epigenetics now refers to regulatory mechanisms of DNA transcription that affect gene expression of which DNA methylation is the most widely studied. The relative role of epigenetics in cancer has been attributed to the observation in 1983 by two laboratories that most cancer DNA has fewer methyl groups than non-cancer DNA [3-5]. In one of these studies, Feinberg and Vogelstein showed that DNA methylation was linked to tissue-specific gene silencing in cancer cells, by finding that a substantial proportion of CpG islands were methylated in normal tissues were unmethylated in cancer cells [3].

Citation analysis is a systematic approach for identifying scientific publications that have a high impact in the scientific or medical community measuring high-impact papers and how they have shaped scientific disciplines [6]. For this purpose, the Institute for Scientific Information collects citation counts for academic journals in the Science Citation Index. Although bibliometric analyses have been performed in the past on cancer and genomics, little is known about the most frequently cited articles specifically related to cancer.
epigenetics [6-10]. Therefore, the purpose of this study is to use citation count to identify those papers in the scientific literature that have made key contributions in the field of cancer epigenetics and identify key driving forces behind future investigations.

**Materials And Methods**

The Thomson Reuters Web of Science (WoS) database was used to query for citations of all articles relevant to cancer epigenetics. The basic search tool was selected, the keyword search for the topic to identify the articles of interest was specified as: “(epigenetic OR epigenomic OR methylation OR hypermethylation OR Cpg island OR chromatic remodeling OR histone modification OR RNA interference OR gene silencing OR promoter regions OR chromatin assembly and disassembly OR liquid biopsy OR molecular OR biomolecular) AND (cancer OR neoplasm)”. The following search parameters were used: 1) articles published in the years 1980-2018 (since the word ‘epigenetics’ was conceived in 1980); 2) all languages; 3) within the Science Citation Index Expanded. The results were carefully reviewed, and only those relevant to cancer epigenetics were selected. All review articles were excluded from the list. The top 100 articles by the number of citations that matched the search criteria were then further analyzed, and the title, first author, journal, and year of publication, number of citations, country, and the institution of origin were recorded. The articles retrieved were sorted in descending order in terms of times cited, and the number of citations per year was calculated.

**Results**

Our query retrieved 234,679 papers (Figure 1).

![Number of publications per year retrieved from the Thomson Reuters Web of Science with the keyword search described in methods](image)

The top 100 articles related to "cancer epigenetics" were identified by the number of times they were cited (Table 1).

| WoS Rank | Authors    | Year | Article title                                                                 | Total number of citations | CY index | CY rank |
|----------|------------|------|------------------------------------------------------------------------------|---------------------------|----------|---------|
| 1        | Golub et al. | 1999 | Molecular classification of cancer: class discovery and class prediction by gene expression monitoring | 7124                      | 375      | 6       |
|   | Authors                          | Year | Title                                                                 | Volume | Issue | Pages |
|---|----------------------------------|------|-----------------------------------------------------------------------|--------|-------|-------|
| 2 | Alizadeh et al.                  | 2000 | Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling | 6045   | 336   | 13    |
| 3 | Herman et al.                    | 1996 | Methylation-specific PCR: a novel PCR assay for methylation status of CpG islands | 4600   | 209   | 26    |
| 4 | Barski et al.                    | 2007 | High-resolution profiling of histone methylations in the human genome   | 3849   | 350   | 10    |
| 5 | Hegi et al.                      | 2005 | MGMT gene silencing and benefit from temozolomide in glioblastoma       | 3394   | 261   | 21    |
| 6 | Chin et al.                      | 2008 | Comprehensive genomic characterization defines human glioblastoma genes and core pathways | 3359   | 336   | 12    |
| 7 | Cerami et al.                    | 2012 | The eBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data | 3354   | 559   | 2     |
| 8 | Stupp et al.                     | 2009 | Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial | 3252   | 361   | 8     |
| 9 | Muzny et al.                     | 2012 | Comprehensive molecular characterization of human colon and rectal cancer | 3157   | 526   | 3     |
| 10| Verhaak et al.                   | 2010 | Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1 | 2891   | 361   | 7     |
| 11| Bell et al.                      | 2011 | Integrated genomic analyses of ovarian carcinoma                      | 2725   | 389   | 5     |
| 12| Gupta et al.                     | 2010 | Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis | 2637   | 330   | 15    |
| 13| Forner et al.                    | 2012 | Hepatocellular carcinoma                                             | 2427   | 405   | 4     |
| 14| Travis et al.                    | 2011 | International association for the study of lung cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of lung adenocarcinoma | 2225   | 318   | 17    |
| 15| Yanaihara et al.                 | 2006 | Unique microRNA molecular profiles in lung cancer diagnosis and prognosis | 2169   | 181   | 27    |
| 16| Curtis et al.                    | 2012 | The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups | 1911   | 319   | 16    |
| 17| Neve et al.                      | 2006 | A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes | 1828   | 152   | 30    |
| 18| Nielsen et al.                   | 2004 | Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma | 1731   | 124   | 42    |
| 19| Hammerman et al.                 | 2012 | Comprehensive genomic characterization of squamous cell lung cancers | 1731   | 289   | 19    |
| 20| Toyoda et al.                    | 1999 | CpG island methylator phenotype in colorectal cancer                  | 1701   | 90    | 58    |
| 21| Takamizawa et al.                | 2004 | Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival | 1695   | 121   | 43    |
| 22| Merlo et al.                     | 1995 | 5′ CpG island methylation is associated with transcriptional silencing of the tumour suppressor p16/CDKN2/MTS1 in human cancers | 1671   | 73    | 72    |
| 23| Ley et al.                       | 2013 | Genomic and epigenetic landscapes of adult de novo acute myeloid leukemia | 1656   | 331   | 14    |
| 24| Varambally et al.                | 2002 | The polycomb group protein EZH2 is involved in progression of prostate cancer | 1625   | 102   | 50    |
| 25| Bhattacharjee et al.             | 2001 | Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses | 1624   | 96    | 52    |
| 26| Esteller et al.                  | 2001 | A gene hypermethylation profile of human cancer                       | 1605   | 94    | 55    |
| 27| Meissner et al.                  | 2008 | Genome-scale DNA methylation maps of pluripotent and differentiated cells | 1538   | 154   | 29    |
| No. | Authors             | Year | Title                                                                 | CitedBy |
|-----|---------------------|------|-----------------------------------------------------------------------|---------|
| 28  | Zhang et al.        | 2007 | microRNAs as oncogenes and tumor suppressors                           | 1515    |
| 29  | Kandoth et al.      | 2013 | Mutational landscape and significance across 12 major cancer types      | 1506    |
| 30  | Cameron et al.      | 1999 | Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer | 1473    |
| 31  | Clark et al.        | 1994 | High sensitivity mapping of methylated cytosines.                      | 1464    |
| 32  | Herman et al.       | 1998 | Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma | 1455    |
| 33  | Bass et al.         | 2014 | Comprehensive molecular characterization of gastric adenocarcinoma      | 1403    |
| 34  | Collisson et al.    | 2014 | Comprehensive molecular profiling of lung adenocarcinoma                | 1372    |
| 35  | Brennan et al.      | 2013 | The somatic genomic landscape of glioblastoma                          | 1367    |
| 36  | Esteller et al.     | 2000 | Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents | 1360    |
| 37  | Weinstein et al.    | 2013 | The cancer genome atlas pan-cancer analysis project                    | 1293    |
| 38  | Weber et al.        | 2007 | Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome | 1289    |
| 39  | Figueroa et al.     | 2010 | Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation | 1280    |
| 40  | Getz et al.         | 2013 | Integrated genomic characterization of endometrial carcinoma            | 1273    |
| 41  | Irizarry et al.     | 2009 | The human colon cancer methylome shows similar hypo- and hypermethylation at conserved tissue-specific CpG island shores | 1267    |
| 42  | Herman et al.       | 1995 | Inactivation of the CDKN2/p16/MTS1 gene is frequently associated with aberrant DNA methylation in all common human cancers. | 1241    |
| 43  | Narita et al.       | 2003 | Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence | 1238    |
| 44  | Herman et al.       | 1994 | Silencing of the VHL tumor-suppressor gene by DNA methylation in renal carcinoma. | 1226    |
| 45  | Swerdlow et al.     | 2016 | The 2016 revision of the World Health Organization classification of lymphoid neoplasms | 1201    |
| 46  | Noushmehr et al.    | 2010 | Identification of a CpG Island methylator phenotype that defines a distinct subgroup of glioma | 1170    |
| 47  | Kane et al.         | 1997 | Methylation of the hMLH1 promoter correlates with lack of expression of hMLH1 in sporadic colon tumors and mismatch repair-defective human tumor cell lines | 1164    |
| 48  | Weisenberger et al. | 2006 | CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer | 1162    |
| 49  | Weber et al.        | 2005 | Chromosome-wide and promoter-specific analyses identify sites of differential DNA methylation in normal and transformed human cells | 1087    |
| 50  | Fraga et al.        | 2005 | Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer | 1060    |
| 51  | Fabbri et al.       | 2007 | MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B | 1041    |
| 52  | Orom et al.         | 2010 | Long noncoding RNAs with enhancer-like function in human cells          | 1041    |
| 53  | Kleer et al.        | 2003 | EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells | 1014    |
| 54  | Weinstein et al.    | 2014 | Comprehensive molecular characterization of urothelial bladder carcinoma | 1014    |
| No. | Authors et al. | Year | Title |
|-----|---------------|------|-------|
| 55  | Jahr et al.   | 2001 | DNA fragments in the blood plasma of cancer patients: quantitations and evidence for their origin from apoptotic and necrotic cells |
| 56  | Hudson et al. | 2010 | International network of cancer genome projects |
| 57  | Costello et al. | 2000 | Aberrant CpG-island methylation has non-random and tumour-type-specific patterns |
| 58  | Gaudet et al. | 2003 | Induction of tumors in mice by genomic hypomethylation |
| 59  | Sharma et al. | 2010 | A Chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations |
| 60  | Esteller et al. | 1999 | Inactivation of the DNA repair gene O-6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia |
| 61  | Zuber et al. | 2011 | RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia |
| 62  | Iorio et al. | 2007 | MicroRNA signatures in human ovarian cancer |
| 63  | Dweep et al. | 2011 | miRWalk - database: prediction of possible miRNA binding sites by "walking" the genes of three genomes |
| 64  | Comijn et al. | 2001 | The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion |
| 65  | Issa et al. | 1994 | Methylation of the oestrogen receptor CpG island links aging and neoplasia in human colon. |
| 66  | Kosaka et al. | 2010 | Secretory mechanisms and intercellular transfer of microRNAs in living cells |
| 67  | Saito et al. | 2006 | Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells |
| 68  | Carroll et al. | 2006 | Genome-wide analysis of estrogen receptor binding sites |
| 69  | Valk et al. | 2004 | Prognostically useful gene-expression profiles in acute myeloid leukemia |
| 70  | Weinstein et al. | 1997 | An information-intensive approach to the molecular pharmacology of cancer |
| 71  | Kantarjian et al. | 2006 | Decitabine improves patient outcomes in myelodysplastic syndromes - results of a phase III randomized study |
| 72  | Houseman et al. | 2012 | DNA methylation arrays as surrogate measures of cell mixture distribution |
| 73  | Patel et al. | 2014 | Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma |
| 74  | West et al. | 2001 | Predicting the clinical status of human breast cancer by using gene expression profiles |
| 75  | Turchinovich et al. | 2011 | Characterization of extracellular circulating microRNA |
| 76  | McCabe et al. | 2012 | EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations |
| 77  | Dammann et al. | 2000 | Epigenetic inactivation of a RAS association domain family protein from the lung tumour suppressor locus 3p21.3 |
| 78  | Turcan et al. | 2012 | IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype |
| 79  | Rhee et al. | 2002 | DNMT1 and DNMT3b cooperate to silence genes in human cancer cells |
| 80  | Lapointe et al. | 2004 | Gene expression profiling identifies clinically relevant subtypes of prostate cancer |
| 81  | Eckhardt et al. | 2006 | DNA methylation profiling of human chromosomes 6, 20 and 22 |
The articles on this top 100 list were cited between 7,124 times (article rank 1) and 720 times (article rank 100). Collectively, the top 100 articles have been cited 147,083 times with a median of 1,050 for each paper, and an interquartile range of 871 - 1610. The oldest article on the top 100 list was from 1993, and the most recent from 2016. In the period 1980-2018, the two most prolific years were 2006 and 2010, with nine articles each among the top 100 most cited articles. In terms of the number of citations per year, the top article had been cited 375 times per year (CY rank number 6). Likewise, the bottom article has been cited 29 times per year (CY rank number 100). A graph of time vs. publication output (Figure 1) indicates that the field of cancer epigenetics has had publications in the range 1994-2014. The most productive decade was

| Rank | Authors            | Year | Title                                                                 | CY | WoS | Citation |
|------|--------------------|------|----------------------------------------------------------------------|----|-----|----------|
| 1    | Bos et al.         | 2009 | Genes that mediate breast cancer metastasis to the brain              | 847| 94  | 56       |
| 2    | Iliopoulos et al.  | 2009 | An epigenetic switch involving NF-kappa B, lin28, let-7 microRNA, and IL6 links inflammation to cell transformation | 845| 94  | 57       |
| 3    | Bracken et al.     | 2006 | Genome-wide mapping of polycomb target genes unravels their roles in cell fate transitions | 842| 70  | 74       |
| 4    | Campo et al.       | 2011 | The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications | 825| 118 | 45       |
| 5    | Chapman et al.     | 2011 | Initial genome sequencing and analysis of multiple myeloma            | 824| 118 | 46       |
| 6    | Murakami et al.    | 2006 | Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues | 815| 68  | 76       |
| 7    | Gregoretti et al.  | 2004 | Molecular evolution of the histone deacetylase family: Functional implications of phylogenetic analysis | 806| 58  | 83       |
| 8    | Li et al.          | 2002 | Causal relationship between the loss of RUNX3 expression and gastric cancer | 805| 50  | 93       |
| 9    | Ng et al.          | 2009 | Differential expression of microRNAs in plasma of patients with colorectal cancer: a potential marker for colorectal cancer screening | 794| 88  | 59       |
| 10   | Bibikova et al.    | 2011 | High density DNA methylation array with single CpG site resolution    | 762| 109 | 49       |
| 11   | Yap et al.         | 2010 | Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a | 760| 95  | 53       |
| 12   | Suzuki et al.      | 2004 | Epigenetic inactivation of SFRP genes allows constitutive WNT signaling in colorectal cancer | 758| 54  | 87       |
| 13   | Esteller et al.    | 2000 | Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors | 756| 42  | 96       |
| 14   | Schlesinger et al. | 2007 | Polycomb-mediated methylation on Lys27 of histone H3 pre-marks genes for de novo methylation in cancer | 748| 68  | 75       |
| 15   | Shimono et al.     | 2009 | Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells | 745| 83  | 62       |
| 16   | Doi et al.         | 2009 | Differential methylation of tissue- and cancer-specific CpG island shores distinguishes human induced pluripotent stem cells, embryonic stem cells and fibroblasts | 744| 83  | 63       |
| 17   | Esteller et al.    | 1999 | Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients | 741| 39  | 97       |
| 18   | Belinsky et al.    | 1998 | Aberrant methylation of p16[INK4a] is an early event in lung cancer and a potential biomarker for early diagnosis | 723| 36  | 99       |
| 19   | Rainier et al.     | 1993 | Relaxation of imprinted genes in human cancer.                        | 720| 29  | 100      |

**TABLE 1: The top 100 most cited articles in cancer epigenetics ranked by number of times cited**

| CY - number of citations per year; WoS - Web of Knowledge |

Citations corresponding to WoS rank are located in appendices.
from 2000 to 2009, producing 49 papers in the Top 100 (Table 2).

| Decade of publication | No. of articles (n=100) |
|-----------------------|------------------------|
| 1970-1979             | 0                      |
| 1980-1989             | 0                      |
| 1990-1999             | 13                     |
| 2000-2009             | 49                     |
| 2010-2019             | 27                     |

**TABLE 2: Decade of publication of top 100 in cancer epigenetics**

The top 100 most cited articles were published in 28 different journals, with the journal Nature contributing the most studies with 22 articles (Table 3).
| Rank | Journal                                                   | No. of articles (n=100) |
|------|-----------------------------------------------------------|-------------------------|
| 1    | Nature                                                    | 22                      |
| 2    | Nature Genetics                                           | 15                      |
| 3    | Proceedings of the National Academy of Sciences of the United States of America | 10                      |
| 4    | Cancer Research                                          | 8                       |
| 4    | Cell                                                      | 8                       |
| 5    | Cancer Cell                                              | 6                       |
| 6    | New England Journal of Medicine                           | 4                       |
| 6    | Science                                                  | 4                       |
| 7    | Blood                                                     | 2                       |
| 7    | Molecular Cell                                            | 2                       |
| 7    | Nucleic Acids Research                                    | 2                       |
| 8    | BMC Bioinformatics                                        | 1                       |
| 8    | Cancer                                                    | 1                       |
| 8    | Cancer Discovery                                          | 1                       |
| 8    | Clinical Cancer Research                                  | 1                       |
| 8    | Developmental Biology                                     | 1                       |
| 8    | Genes Development                                         | 1                       |
| 8    | Genomics                                                  | 1                       |
| 8    | Gut                                                       | 1                       |
| 8    | Journal of the National Cancer Institute                  | 1                       |
| 8    | Journal of Biological Chemistry                           | 1                       |
| 8    | Journal of Biomedical Informatics                         | 1                       |
| 8    | Journal of Molecular Biology                              | 1                       |
| 8    | Journal of Thoracic Oncology                              | 1                       |
| 8    | Lancet                                                    | 1                       |
| 8    | Lancet Oncology                                           | 1                       |
| 8    | Nature Medicine                                           | 1                       |
| 8    | Oncogene                                                  | 1                       |

### TABLE 3: Journals of origin

Seventy-eight percent of the top 100 most cited papers originated in the United States (n=78). The next five countries with the highest number of articles were Germany (n=4), Switzerland (n=4), Japan (n=3), Spain (n=2), and United Kingdom (n=2). Australia, Belgium, Denmark, Israel, Netherlands, China, and South Korea had one article, each among the top 100. Among the 100 most cited papers, there were a total of 77 unique first authors. Collectively, the two authors with the largest number of articles on the top 100 list were Baylin SB and Herman JG with 26 and 20 papers, respectively (Table 4). The next five authors that followed were Getz G, Laird PW, Meyerson M, Sander C, and Weisenberger DJ, each with 13, 12, 12, 12, and 12 articles, respectively.
Among the top 100 cited papers, there were three clinical trials, two guidelines or society-based recommendations, 18 cancer classifications, 11 articles related to research tools or methods, 55 articles related to epigenetic cancer mechanism, nine papers related to epigenetic cancer markers/screening/diagnosis and five papers related to epigenetics and cancer treatment (Table 5).

### TABLE 4: Top five authors appearing in top 100 list

| Rank | Author          | No. of articles (n=100) |
|------|-----------------|-------------------------|
| 1    | Baylin SB       | 26                      |
| 2    | Herman JG       | 20                      |
| 3    | Getz G          | 13                      |
| 4    | Laird PW        | 12                      |
| 4    | Meyerson M      | 12                      |
| 4    | Sander C        | 12                      |
| 4    | Weisenberger DJ | 12                      |
| 5    | Ding L          | 11                      |
| 5    | Hayes DN        | 11                      |
| 5    | Lander ES       | 11                      |
| 5    | Perou CM        | 11                      |
|   | Authors                | Year | Title                                                                                           | Page |
|---|------------------------|------|-------------------------------------------------------------------------------------------------|------|
|18 | Nielsen et al.         | 2004 | Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma | 1731 |
|20 | Toyota et al.          | 1999 | CpG island methylator phenotype in colorectal cancer                                             | 1701 |
|23 | Ley et al.             | 2013 | Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia                        | 1656 |
|25 | Bhattacharjee et al.   | 2001 | Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses | 1624 |
|29 | Kandoth et al.         | 2013 | Mutational landscape and significance across 12 major cancer types                              | 1506 |
|35 | Brennan et al.         | 2013 | The somatic genomic landscape of glioblastoma                                                   | 1367 |
|39 | Figueroa et al.        | 2010 | Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation | 1280 |
|45 | Swerdlow et al.        | 2016 | The 2016 revision of the World Health Organization classification of lymphoid neoplasms       | 1201 |
|46 | Noushmehr et al.       | 2010 | Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma | 1170 |
|48 | Weisenberger et al.    | 2006 | CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer | 1162 |
|78 | Turcan et al.          | 2012 | IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype                  | 854  |
|80 | Lapointe et al.        | 2004 | Gene expression profiling identifies clinically relevant subtypes of prostate cancer            | 849  |
|85 | Campo et al.           | 2011 | The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications | 825  |
|15 | Yanaihara et al.       | 2006 | Unique microRNA molecular profiles in lung cancer diagnosis and prognosis                        | 2169 |
|21 | Takamizawa et al.      | 2004 | Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival | 1695 |

EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation.
**Discussion**

In this study, we sought to identify the most cited 100 articles regarding cancer epigenetics, to gain insight into the history and future directions of this rapidly growing scientific field.

The article that received the most citations on the top 100 list was "Molecular classification of cancer: class discovery and class prediction by gene expression monitoring" [11]. This paper was cited 7,340 times, with an average of 408 citations per year since publication. At the time, the paper was notable for developing the first generalized approach for identifying new cancer classes by applying gene expression profiling to distinguish between acute myeloid leukemia (AML) versus acute lymphoblastic leukemia (ALL). This study marked the beginning of gene expression-based cancer therapy. Currently, the European LeukemiaNet classification in AML uses cytogenetic and molecular data to identify the AML prognostic groups [12-14].

Since the first epigenetic abnormality was identified in cancer cells in 1983, multiple advances led to improved knowledge in epigenetics and cancer [3-5]. DNA methylation has been defined as an example of epigenetic dysregulation in cancer, with both hypomethylation and hyper-methylation having significant roles. DNA hypomethylation can lead to gene activation, and it is linked to chromosomal instability [15, 16]. DNA hypermethylation has been associated with gene silencing as a tumor-suppressor silencing cancer mechanism given that it has been found when genes are rarely mutated but that are frequently DNA hypermethylated and silenced in cancer [17-20]. Histone modification is another epigenetic cancer-linked mechanism that controls chromatin structure [21, 22]. As a result, the detection of epigenetic changes, such as abnormal promoter CpG island DNA hypermethylation, has been studied as a potential biomarker strategy for assessing cancer risk, early detection, prognosis and predicting therapeutic responses [23, 24]. The list of potential marker genes, knowledge of their position in cancer progression, and the development of ever more sensitive epigenetic detection strategies, including nanotechnology approaches, are all expanding [25, 26]. All these landmark discoveries led to the elucidation of novel cancer biomolecular
mechanisms, new scientific research tools, and the development of new epigenetic-based targeted therapeutic avenues. As a result of that, "The National Institutes of Health (NIH) Roadmap Epigenomics Mapping Consortium" is accelerating the understanding of epigenomics in human health and disease together with the ENCODE Project (ENCylopedia Of DNA Elements) [27, 28]. The most immediate future of this new exciting scientific field includes the development of liquid biopsies, personalized medicine, and targeted therapies.

Although citation analysis is a useful tool with the potential benefit of insight into literature trends, it is not without limitations. Over half a century has passed since the Science Citation Index (SCI) was launched as the first systematic effort to track citations in the scientific literature [29]. We recognize that citation counts have inherent biases and that they are not purely quantifiable systems to rank papers by their impact in the scientific literature. In an attempt to control for some of these inherent and potential biases, we utilized the citations per year index in addition to the total number of citations per paper. Despite that, older publications have had a longer timespan to accumulate citations giving them a distinct advantage over newer and potentially more relevant studies. Lastly, one hundred is an arbitrary number since the landmark articles in epigenetic research did not accumulate enough citations such as the paper by Gama-Sosa, Slagel, Trewyn, et al. “The 5-methylcytosine content of DNA from human tumors” that only had 574 citations [30]. Although metrics such as citation counts do have flaws, in the current era, they also serve as one way to measure objectively impact of an article in the scientific community.

Conclusions

In this study, the 100 most cited articles in cancer epigenetics were examined, and the contributions from various authors, specialties, and countries were identified. Cancer epigenetics is a rapidly growing scientific field impacting translational research in cancer screening, diagnosis, classification, prognosis, and targeted treatments. Recognition of important historical contributions to this field may guide future investigations.

Appendices

References from Table 1 and Table 5
1. Golub TR, Slonim DK, Tamayo P, et al.: Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science. 1999, 286:531-537. 10.1126/science.286.5439.531

2. Alizadeh AA, Eisen MB, Davis RE, et al.: Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000, 403:503-511. 10.1038/3500501

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**Additional Information**

**Disclosures**

**Human subjects:** All authors have confirmed that this study did not involve human participants or tissue.

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