Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2022;31:127-133
doi: 10.15570/actaapa.2022.22

Analysis of top-cited articles on melanoma

Ka Siu Fan[1]✉, Ka Hay Fan[2], Pak Lim Tse[2], Hao Ding[2], Runqing Su[3], Hiu Tat Kwok[4]

[1]Royal Surrey County Hospital, Guildford, United Kingdom. [2]Faculty of Medicine, Imperial College, London, United Kingdom. [3]Bristol Medical School, University of Bristol, Bristol, United Kingdom. [4]Queen's Medical Centre, Nottingham, United Kingdom.

Abstract

Introduction: This bibliometric analysis evaluates the most influential studies in clinical research on melanoma.
Methods: Based on the bibliometric theory, articles in the Thomson Reuters Web of Science database were analyzed. Full English-language articles were searched for using the terms *melanoma*, *superficial spreading melanoma*, *nodular melanoma*, *lentigo maligna melanoma*, and *acral lentiginous melanoma*. The 100 most-cited articles were analyzed by topic, author, journal of publication, year of publication, institution, and country of origin.
Results: The search returned 243,109 articles, with the majority from the past 3 decades: 1991–2000 (n = 29), 2001–2010 (n = 28), and 2011–2020 (n = 30). The top 100 cited articles had mean and median citations of 2,159 and 1,793, respectively. An article on the use of ipilimumab in metastatic melanoma, by Hodi et al., was most cited (8,150). The *New England Journal of Medicine* had the most citations (58,489), and *Nature* published the most articles (n = 21). The United States published the most articles (n = 81), led by the National Cancer Institute (n = 16). The majority of articles explored management (n = 68), prognosis (n = 57), and immunotherapy (n = 27).
Conclusions: This analysis serves as a guide for future research and highlights key areas of research, particularly in genetics and immunotherapy, that have influenced current knowledge of melanoma.

Keywords: bibliometrics, bibliometric analysis, melanoma, metastatic melanoma

Received: 17 July 2022 | **Returned for modification:** 7 October 2022 | **Accepted:** 9 November 2022

Introduction

Melanoma is the most aggressive skin cancer. It originates from melanocytes and has a variety of subtypes, such as superficial spreading melanoma, lentigo maligna, acral lentiginous melanoma, and nodular melanoma (1). Although it is predominantly associated with ultraviolet exposure, genes such as *CDKN2A* and *CDK4* also contribute to the formation of melanoma (2). In 2018, the World Health Organization reported more than 1.3 million new cases of skin cancer, of which more than one in five were melanoma (3). The countries with the highest melanoma rates, such as Australia and New Zealand, report an incidence as high as 33.6 per 100,000 population and mortalities reaching 3.4 per 100,000. Despite contributing to only 3% of all skin cancers, its tendency to metastasize makes it particularly lethal, evidenced by melanoma causing up to 65% of all skin cancer deaths (4). Fortunately, through rigorous awareness campaigns in recent decades, melanoma continues to remain the focus of attention in both public awareness and research (5, 6). Although its treatment options traditionally include surgery, chemotherapy, and radiotherapy, the last decade of advances in immunotherapy and targeted therapy has already improved how the disease is tackled (7). To fully evaluate the progress made in melanoma research and its potential future directions, a bibliometric analysis of the most influential work on it can be used.

The study of tracking scientific advances and progress plays a role in improving the diagnosis and management of various diseases. Bibliometric analysis, a method first proposed by Pritchard, uses statistical means to identify the nature and distribution of scientific information (8). Through measurements of citation patterns in scientific literature, the academic significance and impact of research can be extrapolated from its citation count and journal impact factor. The examination of past and future trends can also help researchers identify and understand the latest developments in their field of interest. This has been utilized across various specialties to analyze the most influential works, including general surgery and surgical subspecialities (9–14). There has not been any recent citation analysis for melanoma, and therefore this study provides a perspective on developments and directions in this field (15).

Methods

The Thomson Reuters Web of Science citation indexing database was used to conduct the search. The keywords *melanoma*, *superficial spreading melanoma*, *nodular melanoma*, *lentigo maligna melanoma*, and *acral lentiginous melanoma* were searched across all fields for all documents in the entire database to maximize the return of eligible articles. No restrictions were applied on the publication year or study design of articles. The recorded citation count for the indexing databases is as follows: Science Citation Index Expanded, Social Sciences Citation Index, Conference Proceedings Citation Index—Science, Conference Proceedings Citation Index—Social Science & Humanities, and Emerging Sources Citation Index. The literature returned was sorted by citation count to extract the top 100 cited articles, a method initially developed by Paladugu et al. (16).

Only full articles in English were included; abstracts or letters were excluded. Only articles that included melanoma-specific issues, such as pathogenesis, treatments, or outcomes, were eligible. Articles that focused on global mortality or cancers as a whole were excluded. Information on the articles identified, including journal, authorship, institution, country, year of publication, and article type, were extracted. Clarivate Journal Citation Reports was

✉ Corresponding author: fankasiu@gmail.com

used to extract the 2021 journal impact factor, 5-year impact factor, and 2021 eigenfactor of each journal. The citation rate was also calculated by dividing the citation count by the number of years since an article's publication date. The retrieved records were all screened, sorted, and analyzed with Excel.

Results

The literature search was conducted on May 17th, 2021, and it returned 243,109 full-length English-language articles. The top 100 most-cited articles were analyzed for various characteristics over the subsequent 4 weeks.

Sixty-four top-cited articles were excluded because they focused on genetics, pathogenesis, or epidemiology of cancers without coverage of melanoma specifically. The total citation count was 215,902, with a median and mean of 1,793 and 2,159, respectively. Seventy-nine were original articles and 21 were reviews. Pathogenesis and genetics were the topics most studied (n = 68), followed by management and outcomes (n = 57). Twenty-seven articles explored the role of immunotherapy and antibody-based therapies, six studied target therapy, such as proto-oncogene B-Raf (BRAF) and mitogen-activated protein kinase (MAPK) inhibitors, and only two focused on surgical resection.

Within the top 100 cited articles, the citation counts ranged from 1,231 for "Systematic identification of genomic markers of drug sensitivity" by Garnett et al. to 8,150 for "Improved survival with ipilimumab in patients with metastatic melanoma" by Hodi et al. (17, 18). The third most-cited article, by Topalian et al., had the highest citation rate: 741 (19). The oldest article was "The histogenesis and biologic behavior of primary human malignant melanomas of the skin," published in 1969 by Clark et al., whereas the most recent was "Dermatologist level classification of skin cancer with deep neural networks" by Esteva et al., published in 2017 (20, 21). They had 1,847 and 1,941 citations respectively. Table 1 displays the top 100 articles and their respective citation counts and rates. The majority of articles and citations were from the past three decades: 1991–2000 (n = 29; 50,738), 2001–2010 (n = 28; 67,361), and 2011–2020 (n = 30; 74,827). Figure 1 shows the distribution of articles and citations by decade.

The top 100 articles were published across 31 journals, which published between one and 21 articles. *Nature* (n = 21) published the greatest number of articles within the top 100 and had the highest normalized eigenfactor (238.12). *The New England Journal of Medicine* received the greatest number of citations (58,489) and had the third-highest impact factor (176.08). *CA: A Cancer Journal for Clinicians* had the highest impact factor (286.13) and contributed one article with 2,334 citations. Table 2 displays the citation count, articles, and the various journal metrics.

The most highly cited first authors included Hodi (n = 1; 8,150), Robert (n = 3; 8,088), and Topalian (n = 2; 7,990). Rosenberg contributed to the greatest number of articles as first author (n = 4) and received a total of 7,698 citations. Antoni Ribas, the director of the Tumor Immunology Program at the Jonsson Comprehensive Cancer Center and Chair of the Melanoma Committee at SWOG, published the most articles (n = 5) as senior author, with a total of 10,512 citations. Table 3 summarizes the top first and senior authors within the top 100 articles.

The United States had the most citations (171,333), as well as the greatest number of articles (n = 81). The United Kingdom ranked second, with 16,893 citations from six articles. The top four institutions cited were the National Cancer Institute (n = 16; 29,143), Johns Hopkins University School of Medicine (n = 9; 27,169), Memorial Sloan Kettering Cancer Center (n = 5; 12,190), and Broad Institute of MIT and Harvard (n = 4; 8,392), all of which are based in the United States. Table 4 and Figure 2 provide an overview of the top countries and institutions that contributed to the top 100 cited articles.

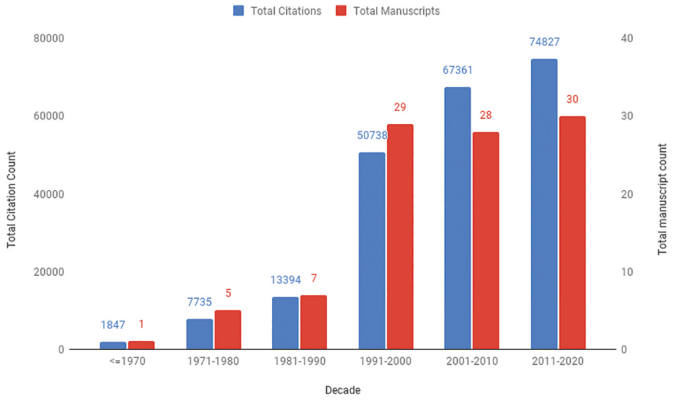

Figure 1 | Articles and citation count by decade.

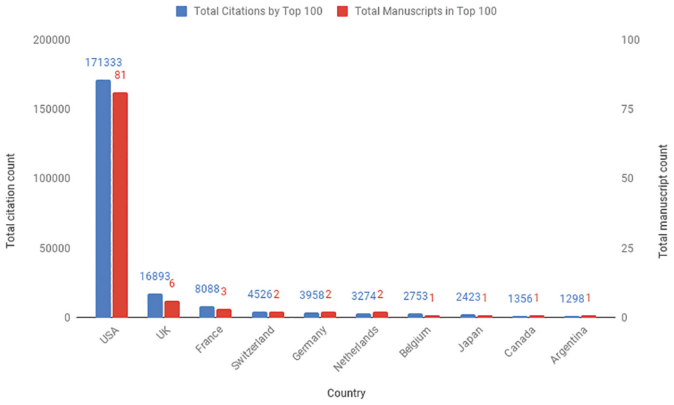

Figure 2 | Top countries by total citation and articles.

Discussion

Among the top 100 articles surveyed, pathogenesis and associated risk factors of melanoma were discussed in the greatest quantity, seen in 68 of the 100 articles. This reflects that the majority of the most important literature was the various discoveries that furthered understanding of how and why melanoma develops. This culminated in a trend to explore the role of immunotherapy and the BRAF/MAPK pathway since the beginning of the 1990s. In comparison, only 16 articles focused on the diagnostic aspect of melanoma. As melanoma remains primarily a clinical diagnosis, the emphasis is properly placed on furthering its treatment. Of those that discussed investigation and diagnosis, seven articles explored the histology and intraoperative analysis of the biopsies, most notably the works of Clark et al. and Breslow, which provides a foundation for estimating melanoma prognosis. Of the specific therapeutic options, this analysis has identified the increasingly dominant trend in the use of immunotherapy and monoclonal antibodies (n = 27). In addition, the last decade also saw increased attention to BRAF and MAPK inhibitors (n = 5), both of which dwarf the representation of surgery (n = 2). The significance of these trends is reflected by the topics covered by the top five cited studies, with three on immunotherapy and two on targeted therapy of BRAF/MAPK. However, although only two articles focused on surgical treatment, it is important to note that metastasectomy

Table 1 | **Top 100 articles ranked by total citation count.**

Rank	Author(s)	Journal	Year	Total citations	Citation rate
1	Hodi et al.	*The New England Journal of Medicine*	2010	8,150	741
2	Davies et al.	*Nature*	2002	6,822	359
3	Topalian et al.	*The New England Journal of Medicine*	2012	6,654	739
4	Pardoll	*Nature Reviews Cancer*	2012	5,379	598
5	Chapman et al.	*The New England Journal of Medicine*	2011	4,932	493
6	Brahmer et al.	*The New England Journal of Medicine*	2012	4,250	472
7	Muller et al.	*Nature*	2001	4,105	205
8	Larkin et al.	*The New England Journal of Medicine*	2015	3,554	592
9	Morton et al.	*Archives of Surgery*	1992	3,153	109
10	Barretina et al.	*Nature*	2012	3,037	337
11	Alley et al.	*Cancer Research*	1988	3,001	91
12	Balch et al.	*Journal of Clinical Oncology*	2009	2,988	249
13	Kamb et al.	*Science*	1994	2,854	106
14	Kalluri et al.	*Nature Reviews Cancer*	2006	2,834	189
15	Robert et al.	*The New England Journal of Medicine*	2011	2,794	279
16	Dong et al.	*Nature Medicine*	2002	2,788	147
17	Renehan et al.	*The Lancet*	2008	2,760	212
18	Vanderbruggen et al.	*Science*	1991	2,753	92
19	Robert et al.	*The New England Journal of Medicine*	2015	2,720	453
20	Schreiber et al.	*Science*	2011	2,669	267
21	Wolchok et al.	*The New England Journal of Medicine*	2013	2,582	323
22	Robert et al.	*The New England Journal of Medicine*	2015	2,574	429
23	Flaherty et al.	*The New England Journal of Medicine*	2010	2,501	227
24	Dranoff et al.	*Proceedings of the National Academy of Sciences of the United States of America*	1993	2,501	89
25	Tumeh et al.	*Nature*	2014	2,496	357
26	Nestle et al.	*Nature Medicine*	1998	2,460	107
27	Kato et al.	*Nature*	2006	2,423	162
28	Grimm et al.	*Journal of Experimental Medicine*	1982	2,420	62
29	Herbst et al.	*Nature*	2014	2,363	338
30	Rosenberg et al.	*The New England Journal of Medicine*	1985	2,354	65
31	Miller et al.	*CA: A Cancer Journal for Clinicians*	2016	2,334	467
32	Flaherty et al.	*The New England Journal of Medicine*	2012	2,268	252
33	Hamid et al.	*The New England Journal of Medicine*	2013	2,215	277
34	Salomon et al.	*Critical Reviews in Oncology Hematology*	1995	2,189	84
35	Rosenberg et al.	*Nature Medicine*	2004	2,128	125
36	Friedl et al.	*Nature Reviews Cancer*	2003	2,108	117
37	Irmler et al.	*Nature*	1997	2,066	86
38	Shalem et al.	*Science*	2014	2,020	289
39	Dudley et al.	*Science*	2002	2,020	106
40	Giuliano et al.	*Annals of Surgery*	1994	2,012	75
41	Clynes et al.	*Nature Medicine*	2000	2,005	95
42	Beroukhim et al.	*Nature*	2010	1,966	179
43	Snyder et al.	*The New England Journal of Medicine*	2014	1,958	280
44	Esteva et al.	*Nature*	2017	1,941	485
45	Balch et al.	*Journal of Clinical Oncology*	2001	1,928	96
46	Wolchok et al.	*Clinical Cancer Research*	2009	1,909	159
47	Breslow	*Annals of Surgery*	1970	1,853	36
48	Hauschild et al.	*The Lancet*	2012	1,850	206
49	Clark et al.	*Cancer Research*	1969	1,847	36
50	Rejman et al.	*Biochemical Journal*	2004	1,828	108
51	Nobori et al.	*Nature*	1994	1,758	65
52	Morgan et al.	*Science*	2006	1,750	117
53	Davis et al.	*Nature*	2010	1,738	158
54	Peinado et al.	*Nature Medicine*	2012	1,731	192
55	Curtin et al.	*The New England Journal of Medicine*	2005	1,699	106
56	Rosenberg et al.	*The New England Journal of Medicine*	1988	1,697	51
57	Brahmer et al.	*Journal of Clinical Oncology*	2010	1,694	154
58	Szatrowski et al.	*Cancer Research*	1991	1,693	56
59	Liotta et al.	*Nature*	1980	1,685	41
60	Balch et al.	*Journal of Clinical Oncology*	2001	1,680	84
61	Mellman et al.	*Nature*	2011	1,657	166
62	DeRisi et al.	*Nature Genetics*	1996	1,650	66
63	Dunn et al.	*Immunity*	2004	1,592	94
64	Boehm et al.	*Nature*	1997	1,569	65
65	Brash et al.	*Proceedings of the National Academy of Sciences of the United States of America*	1991	1,559	52
66	Kirkwood et al.	*Journal of Clinical Oncology*	1996	1,541	62
67	Poste et al.	*Nature*	1980	1,532	37

Table 1 | **Continued.**

Rank	Author(s)	Journal	Year	Total citations	Citation rate
68	Bittner et al.	*Nature*	2000	1,530	73
69	Postow et al.	*The New England Journal of Medicine*	2015	1,529	255
70	Rosenberg et al.	*Nature Medicine*	1998	1,519	66
71	Sosman et al.	*The New England Journal of Medicine*	2012	1,489	165
72	Michaloglou et al.	*Nature*	2005	1,446	90
73	Nazarian et al.	*Nature*	2010	1,415	129
74	Stetler-Stevenson et al.	*Annual Review of Cell Biology*	1993	1,407	50
75	Attele et al.	*Biochemical Pharmacology*	1999	1,402	64
76	Maniotis et al.	*The American Journal of Pathology*	1999	1,397	64
77	Fidler	*Nature New Biology*	1973	1,378	29
78	Hodis et al.	*Cell*	2012	1,369	152
79	Weber et al.	*The Lancet Oncology*	2015	1,364	227
80	Brooks et al.	*Cell*	1996	1,358	54
81	Chambers et al.	*Journal of the National Cancer Institute*	1997	1,356	57
82	Steeg et al.	*Journal of the National Cancer Institute*	1988	1,352	41
83	Topalian et al.	*Journal of Clinical Oncology*	2014	1,336	191
84	Serrano et al.	*Cell*	1996	1,320	53
85	Nelson et al.	*Journal of Clinical Oncology*	2000	1,312	62
86	West et al.	*The New England Journal of Medicine*	1987	1,305	38
87	Kamijo et al.	*Cell*	1997	1,302	54
88	Gomez et al.	*European Journal of Cell Biology*	1997	1,298	54
89	Atkins et al.	*Journal of Clinical Oncology*	1999	1,294	59
90	Bingle et al.	*Journal of Pathology*	2002	1,292	68
91	Dougherty et al.	*Cancer Research*	1978	1,287	30
92	Quintana et al.	*Nature*	2008	1,276	98
93	Gajewski et al.	*Nature Immunology*	2013	1,271	159
94	Roberts et al.	*Proceedings of the National Academy of Sciences of the United States of America*	1985	1,265	35
95	Morton et al.	*The New England Journal of Medicine*	2006	1,264	84
96	Taube et al.	*Science Translational Medicine*	2012	1,260	140
97	Zhang et al.	*Nature Biotechnology*	2006	1,257	84
98	Clark et al.	*Nature*	2000	1,246	59
99	Gearing et al.	*Immunology Today*	1993	1,234	44
100	Garnett et al.	*Nature*	2012	1,231	137

Table 2 | **Journal metrics of the top 100 articles.**

Rank	Journal	Total citations	Total articles	2021 impact factor	5-year impact factor	Normalized eigenfactor
1	*The New England Journal of Medicine*	58,489	20	176.08	125.16	161.02
2	*Nature*	45,302	21	69.50	63.58	238.12
3	*Science*	14,066	6	63.80	59.92	191.93
4	*Journal of Clinical Oncology*	13,773	8	50.77	38.80	51.81
5	*Nature Medicine*	12,631	6	87.24	68.31	49.70
6	*Nature Reviews Cancer*	10,321	3	69.80	78.98	11.39
7	*Cancer Research*	7,828	4	13.31	13.68	19.34
8	*Cell*	5,349	4	66.85	59.90	114.11
9	*Proceedings of the National Academy of Sciences of the United States of America*	5,325	3	12.78	13.45	158.17
10	*The Lancet*	4,610	2	202.73	130.84	120.97
11	*Annals of Surgery*	3,865	2	13.79	12.43	12.21
12	*Archives of Surgery*	3,153	1	4.93	4.89	2.11
13	*Journal of the National Cancer Institute*	2,708	2	13.76	14.54	N/A
14	*Journal of Experimental Medicine*	2,420	1	17.58	16.42	12.64
15	*CA: A Cancer Journal for Clinicians*	2,334	1	286.13	34.26	20.74
16	*Critical Reviews in Oncology Hematology*	2,189	1	6.625	6.59	2.72
17	*Clinical Cancer Research*	1,909	1	13.80	13.98	25.59
18	*Biochemical Journal*	1,828	1	3.77	4.96	3.24
19	*Nature Genetics*	1,650	1	41.38	39.32	34.91
20	*Immunity*	1,592	1	43.47	39.54	26.21
21	*Annual Review of Cell and Developmental Biology*	1,407	1	11.90	18.48	1.78
22	*Biochemical Pharmacology*	1,402	1	6.10	6.19	3.69
23	*The American Journal of Pathology*	1,397	1	5.77	5.48	3.05
24	*Nature New Biology*	1,378	1	N/A	N/A	N/A
25	*The Lancet Oncology*	1,364	1	54.43	49.20	29.47
26	*European Journal of Cell Biology*	1,298	1	6.02	4.16	0.37
27	*Journal of Pathology*	1,292	1	9.88	8.84	3.14
28	*Nature Immunology*	1,271	1	31.25	31.00	17.25
29	*Science Translational Medicine*	1,260	1	19.36	22.18	19.54
30	*Nature Biotechnology*	1,257	1	68.16	60.20	33.19
31	*Immunology Today*	1,234	1	12.86	N/A	N/A

Table 3 | **Most-cited authors in the top 100 articles.**

Rank	First author	Total citations	Articles
1	Hodi, FS	8,150	1
2	Robert, C	8,088	3
3	Topalian, SL	7,990	2
4	Rosenberg, SA	7,698	4
5	Davies, H	6,822	1
6	Balch, CM	6,596	3
7	Brahmer, JR	5,944	2
8	Pardoll, DM	5,379	1
9	Chapman, PB	4,932	1
10	Flaherty, KT	4,769	2
Rank	**Senior author**	**Total citations**	**Articles**
1	Ribas, A	10,512	5
2	Sznol, M	9,236	2
3	Urba, WJ	8,150	1
4	Hodi, FS	7,137	4
5	Futreal, PA	6,822	1
6	Wolchok, JD	6,348	2
7	McArthur, GA	4,932	1
8	Schadendorf, D	4,728	2
9	Chapman, PB	4,351	2
10	Wigginton, JM	4,250	1

Table 4 | **Institutes with the most articles.**

Institution	Country	Total citations	Total articles
National Cancer Institute	USA	29,143	16
Johns Hopkins University School of Medicine	USA	27,169	9
Memorial Sloan Kettering Cancer Center	USA	12,910	5
Broad Institute of MIT and Harvard	USA	8,392	4
Institute Gustave Roussy	France	8,088	3
Howard Hughes Medical Institute	USA	3,868	3
Washington University School of Medicine	USA	4,261	2
Massachusetts General Hospital	USA	4,115	2
Yale School of Medicine	USA	3,922	2
University of California Los Angeles	USA	3,911	2
University of Pennsylvania	USA	3,879	2
Stanford University	USA	3,591	2
Vanderbilt University Medical Center	USA	2,801	2

may still have a role in management and was shown to improve long term outcomes in the 2012 MSLT-1 trial (22). Novel melanoma vaccine treatments also received some attention in the 2000s; however, only four were highly cited, and they were all published before this decade. This under-representation may reflect the lack of breakthroughs as significant as the potential shown by immunotherapy or BRAF/MAPK.

The most-cited melanoma study was published in *The New England Journal of Medicine* in 2010, by Hodi et al. It explores the efficacy of ipilimumab (BMS-734016), a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, to improve survival rates of patients with prior treatment for metastatic melanoma (18). This study was significant at the time because the options for metastatic melanoma were very limited beyond first-line chemotherapy with dacarbazine. In addition, no randomized trials identified alternative treatments with a significant increase in survival rates at the time (23). Its blockade of the inhibitory activity of CTLA-4 allowed the upregulation of T-cell activities to enhance the anticancer effect of the immune system, which unfortunately also led to side effects such as diarrhea, colitis, injection site reactions, and vitiligo (18). Given the potential of ipilimumab demonstrated by previous phase 2 trials, Hodi et al. conducted the first phase 3 trial for a metastatic melanoma therapy (24). With glycoprotein gp100 as a control, ipilimumab was found to improve survival rates regardless of cancer peptide vaccination status and to extend median overall survival rates from 6.4 months to 10 (18, 25). Despite strong and potentially life-threatening immune-mediated side effects, this study highlighted the survival benefits of ipilimumab, which has since been approved by the American FDA and British NICE guidelines as a treatment for metastatic melanoma. The use of ipilimumab likely contributed to the reduction in long-term melanoma mortality seen between 2013 and 2017, whereby metastatic melanoma mortality in the US alone decreased by 5.7% and 7% in patients above and below age 50, respectively (26).

Similarly, efforts in seeking alternative immunotherapy targets led to studying the efficacy of PD-1 inhibitors in augment T-cell activity in melanoma. The third most-cited article investigated the use of nivolumab (BMS-936558) and was published in *The New England Journal of Medicine* in 2012 by Topalian et al., with Hodi also as a coauthor (19). The study evaluated the use of this anti-PD-1 antibody in promoting antitumor activity in patients with selected advanced cancer, and it found that 28% of patients with advanced melanoma responded to the treatment. In comparison to other conventional treatments, such as chemotherapy and tyrosine kinase inhibitors, the durability of anti-PD-L1 antibody therapy appears to be greater (19). Furthermore, this study was frequently cited due to its impact on promoting future studies on anti-PD-1 antibody, including being the groundwork for a phase 3 study by Robert et al. in 2015, which further corroborated the therapeutic benefits of nivolumab over standard chemotherapy in advanced melanoma (27). Moreover, the work of Hodi et al. and Topalian et al. led to the combined use of ipilimumab and nivolumab in a phase 1 trial in 2017 that showed manageable safety profiles while offering superior clinical responses (28). Hence, the significance of these two studies can be quantified by having the two highest citation rates of 741 and 739 despite being relatively recent. Together these two studies have significantly influenced both the knowledge and management of melanoma, and they have laid the foundation for future efforts to optimize the use of immunotherapy in advanced melanoma.

The rise of targeted therapy offered a potential alternative to immunotherapy. This includes targeting BRAF/MAPK, which has been identified as important mutations in oncogenesis (29). The second most-cited melanoma study was published in *Nature* in 2002 by Davies et al., and it identified the prevalence of the BRAF/MAPK pathway mutation in melanoma (30). Neoplastic cell lines were screened for mutations to identify 43 probable oncogenic BRAF/MAPK mutations in exons 11 and 15, which were present in 20 out of 34 melanoma cases. It was proposed that BRAF/MAPK mutations in melanoma primarily affected a melanocyte-specific proliferation and differentiation signaling pathway, which accounts for a significantly higher frequency of BRAF/MAPK mutation in melanoma compared to other cancers. Unlike other BRAF/MAPK mutations, it was specifically determined that the V599 BRAF mutation can bypass the need for RAS mutation and acquire malignant potential in a single step. Furthermore, the association with BRAF/MAPK mutations become more significant because they require fewer post-translational modifications than RAF to achieve maximum kinase activity, making it a more important, and likely effective, therapeutic target. This was the first study that explored BRAF/MAPK inhibition as a potential alternative treatment for melanoma. With the influence of this study, more research on BRAF/MAPK followed, which culminated in the development of targeted therapy with sorafenib, vemurafenib,

and dabrafenib in the following years (29). However, the greatest hurdle for targeted therapy to overcome is its short-lived benefits. It was found that patients usually relapse within the first 2 years of therapy because BRAF/MAPK inhibitors were associated with early acquired resistance (31). In the early 2010s, there was some evidence of being able to overcome the resistance by combinational use with MEK inhibitors, which also provided additional benefits of prolonging median progression-free survival from 6.2 months to 9.9 (31). Nonetheless, although this major limitation likely contributed to its relatively low representation within the top 100 cited articles, breakthroughs in overcoming resistance will likely thrust targeted therapy into the spotlight.

The oldest article was ranked 49th and accumulated 1,847 citations since 1969. The pioneering study by Clark et al. provided a thorough analysis of the various characteristics of melanoma subtypes, including superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma (20). The analysis allowed the establishment of the Clark classification system for the invasiveness of melanoma, which served to improve prognostic estimation. The Clark classification later contributed to the second-oldest article, which introduced the Breslow depth, which is now used universally (32, 33). In contrast, the newest study, by Esteva et al. in 2017, utilizes the latest computing technology to develop a novel neural network to differentiate skin cancers, which produces similar performance levels as specialists (21). As expected, the implications of the study range from improving diagnosis accuracy to increasing access to healthcare. It generated 1,941 citations within 3 years, making it the article with the sixth-highest citation rate (485 citations per year). With the increasing integration of technology into clinical practice, as well as the surge in telemedicine following the COVID-19 pandemic, it is likely that the study will remain of interest and ascend the ranks in coming years (34, 35).

This analysis revealed a significant difference in publication and citation patterns in the last 3 decades compared to before 1990, for which the articles total only 13 and 10.6% of the total citations. This may be explained by the fact that the majority of studies in the 1970s and 1980s focused on the pathogenesis and metastasis of melanoma, which provided the foundation for today's understanding of melanoma. Furthermore, these two decades established the beginnings of immunotherapy by highlighting the potential of immunomodulation through studying the uses of interleukin-2 and lymphocytes (36). Along with the many advances in immunotherapy, research interests have continued to grow since 1990, with many continuing to focus on furthering the understanding of immunotherapy, genetics, antibodies, and molecular mechanisms of oncogenesis (37). In comparison with a bibliometric analysis nearly a decade ago, the rise of immunotherapy has now led to an explosion of citation, and it significantly changes the distribution of the top cited articles. Previously, the most-cited articles were "Technical details of intraoperative lymphatic mapping for early stage melanoma" by Morton et al., followed by the landmark articles by Clark et al. and Breslow, which provided the basis for prognosis (15). These articles were cited 2,384, 1,705, and 1,554 times, respectively, by 2014 and have now become the ninth, 49th, and 47th most-cited articles in this study. These studies on prognosis and surgical techniques are now greatly surpassed by studies on immunotherapy and the *BRAF* gene, being cited between 6,654 and 8,150 times (18, 19, 30). This is indicative of the general trend in this field away from prognostic prediction toward immunological and targeted treatments.

There are several limitations to bibliometric analyses. To account for the effect of time on accumulated citations, a citation rate was also calculated to identify articles that received a significant amount of citation within a short time. This is only partially addressed because a citation count of articles is not necessarily directly proportional to time. Biases such as self-citation and institutional bias have not been accounted for, although these can inflate citation counts and affect the distribution of the top 100 cited articles. The restriction to English-language articles only potentially limits the scope of literature included in the study. In addition, because the Web of Science indexes may not include all eligible articles and subsequent citations, the accuracy of the results may be limited. Finally, the study design likely underrepresents the contributions of authors that coauthored articles without being the first or senior author.

Conclusions

The most-cited articles highlighted in this study describe the genetics and immunosuppression involved in invasive melanoma and the treatment options targeting these mechanisms, which have resulted in the current understanding and management of melanoma. Most articles were published in high-impact journals and have been cited at least 1,200 times, reflecting their quality and influence. This bibliometric analysis provides a reference for the most influential articles on melanoma and can guide researchers and clinicians regarding what makes a "citable" article as well as the trends in this field. The most recent article included was published in 2017, which suggests that ongoing research may significantly alter the top 100 articles over the next 5 to 10 years.

References

1. Gorantla VC, Kirkwood JM. State of melanoma. An historic overview of a field in transition. Hematol Oncol Clin North Am. 2014;28:415–35.
2. Potrony M, Badenas C, Aguilera P, Puig-Butille JA, Carrera C, Malvehy J, et al. Update in genetic susceptibility in melanoma. Ann Transl Med. 2015;3:210.
3. International Agency for Research on Cancer. Melanoma of skin ASR [Internet]. Global Cancer Observatory; 2019. [cited 2021 Sep 15]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/16-Melanoma-of-skin-fact-sheet.pdf.
4. Dzwierzynski WW. Managing malignant melanoma. Plast Reconstr Surg. 2013;132.
5. Cancer Research UK. Skin cancer campaign [Internet]. [cited 2021 Sep 15]. Available from: https://www.cancerresearchuk.org/health-professional/awareness-and-prevention/be-clear-on-cancer/skin-cancer-campaign.
6. Kelly PP. Skin cancer and melanoma awareness campaign. Oncol Nurs Forum. 1991;18:927–31.
7. PDQ Adult Treatment Editorial Board. Melanoma treatment (PDQ®): patient version [Internet]. PDQ Cancer Information Summaries. National Cancer Institute (US); 2002. [cited 2021 Sep 15]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26389388.
8. Kokol P, Blažun Vošner H, Završnik J. Application of bibliometrics in medicine: a historical bibliometrics analysis. Heal Inf Libr J. 2021;38:125–38.
9. Chan J, Mak TLA, Chu TSM, Hui TLY, Kwan LYA. The 100 most cited manuscripts in coronary artery bypass grafting. J Card Surg. 2019;34:782–7.
10. Oo S, Fan KS, Khare Y, Fan KH, Chan J, Lam CM, et al. Top 100 cited manuscripts in aortic valve replacement: a bibliometric analysis. J Card Surg. 2020;35:2943–9.

11. Fan KS, Leung KHC, Fan KH, Chan J. Top 100 most influential manuscripts in congenital abdominal pediatric surgery: a bibliometric analysis. J Indian Assoc Pediatr Surg. 2021;26:6–10.
12. Kwok HT, Van M, Fan KS, Chan J. Top 100 cited articles in male breast cancer: a bibliometric analysis. Breast Dis. 2022;41:15–20.
13. Zhang Y, Yu C. Bibliometric evaluation of publications (2000–2020) on the prognosis of gastric cancer. Inquiry. 2021;58:00469580211056O.
14. Chu TSM, Kwok HT, Chan J, Tse FYF. The 100 most cited manuscripts in head and neck cancer: a bibliometric analysis. J Laryngol Otol. 2019;133:936–42.
15. Joyce CW, Sugrue CM, Joyce KM, Kelly JL, Regan PJ. 100 citation classics in the melanoma literature: a bibliometric analysis. Dermatol Surg. 2014;40:1284–98.
16. Paladugu R, Schein M, Gardezi S, Wise L. One hundred citation classics in general surgical journals. World J Surg. 2002;26:1099–105.
17. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature. 2012;483:570–5.
18. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–23.
19. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–54.
20. Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res. 1969; 29:705–27.
21. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542: 115–8.
22. Howard JH, Thompson JF, Mozzillo N, Nieweg OE, Hoekstra HJ, Roses DF, et al. Metastasectomy for distant metastatic melanoma: analysis of data from the first multicenter selective lymphadenectomy trial (MSLT-I). Ann Surg Oncol. 2012; 19:2547–55.
23. Wróbel S, Przybyło M, Stępień E. The clinical trial landscape for melanoma therapies. J Clin Med. 2019;8:368.
24. Weber J, Thompson JA, Hamid O, Minor D, Amin A, Ron I, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res. 2009;15: 5591–8.
25. Sandru A, Voinea S, Panaitescu E, Blidaru A. Survival rates of patients with metastatic malignant melanoma. J Med Life. 2014;7:572–6.
26. Melanoma Research Alliance. 2020 melanoma mortality rates decreasing despite ongoing increase in incidence—Melanoma Research Alliance [Internet]. 2020 [cited 2021 Sep 15]. Available from: https://www.curemelanoma.org/blog/article/2020-melanoma-mortality-rates-decreasing-despite-ongoing-increase-in-incidence-rates.
27. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372: 320–30.
28. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Safety and clinical activity of combined PD-1 (nivolumab) and CTLA-4 (ipilimumab) blockade in advanced melanoma patients. N Engl J Med. 2013;369:122–33.
29. Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, et al. The role of BRAF V600 mutation in melanoma. J Transl Med. 2012;10:85.
30. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417:949–54.
31. Mackiewicz J, Mackiewicz A. BRAF and MEK inhibitors in the era of immunotherapy in melanoma patients. Wspolczesna Onkol. 2017;2:68–72.
32. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg. 1970;172:902–8.
33. McCarter MD. Melanoma. In: Abernathy's surgical secrets. 7th ed. Philadelphia: Elsevier; 2018. p. 311–8.
34. Elkaddoum R, Haddad FG, Eid R, Kourie HR. Telemedicine for cancer patients during COVID-19 pandemic: between threats and opportunities. Futur Oncol. 2020;16:1225–7.
35. McCall B. Could telemedicine solve the cancer backlog? Lancet Digit Heal. 2020; 2:e456–7.
36. West WH, Tauer KW, Yannelli JR, Marshall GD, Orr DW, Thurman GB, et al. Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. N Engl J Med. 1987;316:898–905.
37. Sahu M, Suryawanshi H. Immunotherapy: the future of cancer treatment. J Oral Maxillofac Pathol. 2021;25:371.