Published in final edited form as:

Cancer Causes Control. 2017 January ; 28(1): 5–12. doi:10.1007/s10552-016-0830-6.

Trends in published meta-analyses in cancer research, 2008 to 2013

Ximena V. Qadir¹, Mindy Clyne², Tram Kim Lam¹, Muin J. Khoury^{1,3}, and Sheri D. Schully^{1,4,*}

¹Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

²Kelly Government Services, Troy, MI, USA

³Office of Public Health Genomics, Centers of Disease Control and Prevention, Atlanta, GA, USA

⁴Office of Disease Prevention, National Institutes of Health, Bethesda, MD, USA

Abstract

In order to capture trends in the contribution of epidemiology to cancer research, we describe an online meta-analysis database resource for cancer clinical and population research and illustrate trends and descriptive detail of cancer meta-analyses from 2008 through 2013. A total of 4,686 cancer meta-analyses met our inclusion criteria. During this 6-year period, a 5-fold increase was observed in the yearly number of meta-analyses. Fifty-six percent of meta-analyses concerned observational studies, mostly of cancer risk, more than half of which were genetic studies. The major cancer sites were breast, colorectal and digestive. This online database for Cancer Genomics and Epidemiology Navigator (CGEN) will be continuously updated to allow investigators to quickly navigate the meta-analyses emerging from cancer epidemiology studies and cancer clinical trials.

Keywords

Meta-analysis; Database; Epidemiology; Clinical Trials

INTRODUCTION

Cancer clinical and population-based research has undergone rapid growth in the past two decades which has been documented by a vast expansion of scientific literature. Navigating this “sea of literature” can be overwhelming and thus scientists are increasingly relying on synthesized publications such as meta-analyses to evaluate the body of evidence, help identify scientific gaps, and guide research, policy and practice. Epidemiology, as a discipline, has provided a scientific foundation for clinical and population studies on a wide

*Correspondence about this article should be sent to schullys@mail.nih.gov, Sheri D. Schully, Ph.D., 6100 Executive Boulevard, Suite 2B03, Phone: 301-451-2695.

Financial support: No financial obligations to disclose.

Authors have no conflict of interests to disclose.

spectrum of topics relevant to cancer etiology, prevention, and control. In 2012, the National Cancer Institute (NCI) and the scientific community established eight recommendations to advance the role of epidemiology in medicine and public health [1]. Expanding “Knowledge Integration (KI)” was one recommendation for enabling research prioritization through knowledge management and synthesis from multiple disciplines, and facilitating translation of scientific findings into evidence-based recommendations. Knowledge synthesis (including meta-analyses) is a key component of KI and is essential for “decrypting” mass quantities of data across various cancer research studies.

Conducting rigorous meta-analyses allow scientists to analyze large datasets and publications and combine different studies using systematic analytic methods. For example, Panagiotou et al has described the power of meta-analyses in genome-wide association (GWA) studies as having the ability to measure minor genetic outcomes for common traits [2]. In addition, performing meta-analysis of genomic studies significantly increases the statistical power when analyzing “weaker signals” [3]. With respect to modifiable risk factors, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) have commissioned coordinated effort on systematic reviews and MAs to assess the state of evidence on food, nutrition, physical activity, body fatness and the prevention of cancer [4].

In clinical medicine, meta-analyses have been utilized to evaluate diagnostic and prognostic markers as well as pharmacologic applications [5]. For example, Ioannidis et al evaluated cancer risks associated with the use of common medications considering inconsistent published conclusions from the field. The umbrella review of meta-analyses suggested that the credibility of meta-analyses research should be assessed to determine if a particular clinical question of interest has been addressed appropriately [6]. To our knowledge, there has never been a systematic effort to create a centralized resource of published meta-analyses in cancer clinical and population research. In this report, we introduce a NCI-supported resource, the Cancer Meta-Analyses Database, as a component of the Cancer Genomics and Epidemiology Navigator (CGEN). The URL and information on using this tool can be found via our previous publication [7] and illustrate the trends and overarching landscape of meta-analyses in cancer clinical and population research from 2008 through 2013.

METHODS

Search strategy

To ascertain human cancer meta-analytical studies published in the scientific literature during the years 2008 through 2013, we searched PubMed [8] using a text query (see Online Resource 1) and the Human Genome Epidemiology (HuGE) Navigator [9]. The HuGE Navigator, a database of published, population-based epidemiologic studies of human genes extracted from PubMed offers study type filtering for meta-analysis. Two reviewers read through abstracts to determine whether the articles met inclusion criteria. For articles without abstracts, full text articles were reviewed.

Inclusion/exclusion criteria

Articles were included if there was a meta-analysis reported on outcomes relevant to the cancer care continuum in humans meeting one or more of the following criteria: 1) risk of disease; 2) diagnostic measure; 3) prognostic measure; 4) treatment of disease, including long-term survival and/or adverse events; and 5) screening for disease. The articles also had to be published in English.

Cancer-related meta-analyses were not included if meta-analyzed data were not derived from human studies, measured short-term treatment outcomes (e.g., length of hospital stay, surgical complications, or treatment-related infection) and systematic reviews without a performed quantitative meta-analysis. Figure 1 presents the search strategy, criteria for selection, and manual coding classification of included articles.

Coding classification

We extracted relevant information (i.e. journal title, year of publication, first author location and cancer-site MESH terms) from the article abstracts. For the present paper, we identified the following cancer sites: breast, colorectal, digestive, prostate, lung, ovarian, renal, skin, hematologic, endometrial, bladder, other (i.e. bone, head and neck), and non-specified cancer (i.e. no mention of specific cancer-site or combination of many types of cancer). When any one article had multiple cancer-site mesh terms, coding was attributed for each.

We manually coded all relevant meta-analyses for the following information:

Study type—We categorized each meta-analysis according to the study type of the original studies that the meta-analysis utilized: (1) observational, (2) clinical trial, (3) both observational and clinical trial labeled as ‘mixed’, or (4) ‘not stated’ (for meta-analyses with conclusive information derived or inferred from the abstract). Meta-analyses coded as “observational” may include case-control, cross-section and prospective cohort studies with no clinical intervention. Meta-analyses coded as “clinical trial” may include randomized and non-randomized control trials. We additionally noted whether meta-analyses of clinical trials restricted their study type to randomized control trials.

Outcome—Each meta-analysis was classified by categories along the cancer care continuum (risk, diagnostic, prognostic, treatment and/or screening). The ‘risk’ coding was assigned to those meta-analyses that assessed any factor associated with cancer risk. ‘Diagnostic’ coding included those meta-analyses that evaluated a diagnostic tool or measurement, such as a biomarker, laboratory and/or radiologic diagnostic methods. ‘Prognostic’ meta-analyses were assigned when any tool or measurement provided information regarding survival and/or aggressiveness of disease. Meta-analyses were coded as ‘treatment’ when any pharmaceutical, radiologic, and/or surgical/transplant clinical applications were evaluated. ‘Screening’ meta-analyses were assigned when the analysis evaluated a cancer-screening or early detection tool.

Exposure—For risk-related meta-analyses, we further assessed whether the type of exposure studied: (i) clinical factor (e.g., pharmaceutical, surgical, and/or); (2) modifiable

factor (e.g., lifestyle factors, modifiable health conditions, occupational or environmental exposures). In addition, if the following were noted in the abstract of the article, these were also coded: (1) genomic (e.g., genetic associations, gene expression, epigenetics, or family history), (2) non-modifiable physiologic measurement, (3) demographic and/or (4) socioeconomic. Treatment-related meta-analyses were further categorized as 'pharmaceutical', 'radiologic', and/or 'surgical/transplant'. The pharmaceutical treatment-related meta-analyses included those studies that measured chemotherapeutic or other pharmaceutical effectiveness, including those measuring adverse side effects of these agents. Radiologic treatment-related meta-analyses included radiotherapy as a treatment method. Surgical/transplant treatment-related meta-analyses were those that measured effectiveness of surgical removal of cancer, and/or effectiveness of transplant as a means of treatment.

Statistical analysis

A non-parametric analysis was performed measuring trends (P_{trend}) across ordered groups (article count by year). Statistical significance was considered at $P < 0.05$. The statistical analysis was performed by Stata/SE 13 software and accessed on June 15, 2015.

RESULTS

Our analytic dataset comprised of 4,686 cancer meta-analyses that met our inclusion criteria from 2008 to 2013. We observed a significant linear trend during this 6-year time period ($P_{\text{trend}} = 0.030$). There was a 5-fold increase in the number of published cancer meta-analyses (from $N = 285$ in 2008 to $N = 1,472$ in 2013 (Figure 2).

Table 1 presents the distribution of the study type, cancer care continuum, and cancer site categories by year. With respect to study type, meta-analyses of observational studies comprised 56% ($N = 2,647$) of the total meta-analyses identified. In the 6-year period, a 6-fold increase of meta-analyses of observational studies was observed and they consistently comprised the majority ($>50\%$) of meta-analyses published per year. Twenty percent of the total meta-analyses published were clinical trials (primarily of randomized controlled trials). We were unable to classify the study type of 21% ($N = 1,010$) of the identified meta-analyses based on review of the abstracts alone.

Risk-associated meta-analyses ($N = 2,632$, 55%) dominated the published meta-analyses from 2008 to 2013 followed by treatment-related meta-analyses ($N = 1,177$, 25%) and prognostic-related meta-analyses ($N = 519$, 11%) (Table 1). There was a marked positive trend ($P_{\text{trend}} = 0.030$) in the publication of risk-related meta-analyses over time with nearly a 6-fold increase from 2008 ($N = 151$) to 2013 ($N = 853$). Between 2008 to 2013, risk-associated meta-analyses comprised of over half (range from 52% to 56%) per year compared to the total article count for each specific year. A nearly 9-fold increase of meta-analyses focused on prognostic outcome was observed from 2008 ($N = 29$, 10%) to 2013 ($N = 224$, 15%). Publications of meta-analyses across different categories followed a positive linear trend that were statistically significant ($P_{\text{trend}} < 0.05$) for all but those meta-analyses that were "diagnostic" ($P_{\text{trend}} = 0.351$) and "screening" ($P_{\text{trend}} = 0.093$).

Figure 3 depicts the selected characteristics of the meta-analyses that were risk-associated. Of the 2,632 meta-analyses that assessed cancer risk: 1,590 (60%) were genomic in nature; 933 (35%) were modifiable risk-factor related; 323 were demographic (12%) measurements; 231 articles (9%) were clinical measurements; 164 (~6%) were non-modifiable risk factors.

The top four cancer sites assessed by meta-analyses from 2008 to 2013 were breast (N=656), colorectal (N=591), digestive (N=557) and lung (N=540) (Table 1). While meta-analyses focused on breast cancer dominated overall, reports on digestive cancers have increased yearly as shown in 2008 (N=32), 2009 (N=48), 2010 (N=59), 2011 (N=75), 2012 (N=143) and 2013 (N=200). We observed a similar trend for meta-analyses focused on colorectal cancer and lung. All trend tests across categories were statistically significant; $P_{\text{trend}} < 0.05$ (Table 1).

When we investigated where meta-analyses were published over the 6-year period, the leading journals publishing cancer meta-analyses was PLoS One (N= 391) with the largest contribution submitted in 2012 (N=111) and 2013 (N=245) followed by Asian Pacific Journal of Cancer Prevention (N=195) and Breast Cancer Research and Treatment (N=188) (Figure 4). The Cochrane Database of Systematic Reviews published 93 meta-analyses all together from 2008 to 2013.

In examining the countries from which meta-analyses were performed, we observed that China was the leading country with the highest number of meta-analyses (N=2,401) within this 6-year time period compared to the U.S. (N=579) (Figure 5).

When meta-analyses assessing underlying therapeutic factors (N=1,177) were stratified by cancer sites, lung, colorectal and breast cancers were the most published meta-analyses that contained a therapeutic component at 16% (N=187), 14% (N=165) and 12% (N=138), respectively. When we examined the types of studies that contained a therapeutic factor, clinical studies were dominant (N=788; 67%) compared to observational studies (N=51; 4%) of total published meta-analyses. Of those meta-analyses that examined an underlying genomic factor (N=1,793), breast cancer was the most common at 17% (N=304) followed by digestive and colorectal cancer at 12% (N=220 and N=216, respectively). Observational studies (N=1,632; 91%) were the prevailing study type used to assess genomic associations. Clinical meta-analyses incorporated genomics marginally (N=31; 2%).

DISCUSSION

In the present paper, we described the overall landscape of meta-analyses in the published literature from 2008 to 2013. Our results indicated a substantial upward trend in the quantity of cancer meta-analyses published in this period, particularly for observational studies on risk-related outcomes. Meta-analyses of breast cancer were the leading cancer site reported. It is not surprising that meta-analyses of breast cancer predominated as the proportion of research dollars allocation for breast cancer is consistently high [10] compared to other common cancers such as lung. The results also showed that the top journals publishing meta-analyses were PLoS One, Asian Pacific Journal of Cancer Prevention, Breast Cancer Research and Treatment.

The rapid growth in meta-analyses was contributed primarily by researchers from China followed by the United States which corroborated a previous study that also showed the explosive productivity rate of meta-analyses in biomedical research, specifically in the field of genetic epidemiology [11]. Meta-analyses increase power. Many individual studies are too small to detect small effects, but when combined there is a higher probability of detecting an effect. Secondly, meta-analyses improve precision. In addition, meta-analyses settle controversies arising from conflicting studies. Statistical analysis of findings allows the degree of conflict to be evaluated, and different results to be measured.

The described meta-analysis database in the present paper is an added feature to the Cancer Genomics and Epidemiology Navigator (CGEN). In 2013, the Epidemiology and Genomics Research Program (EGRP) at the National Cancer Institute (NCI) launched CGEN as a resource for the extramural communities, including EGRP grantees. CGEN is an updated and searchable online tool intended to facilitate cancer epidemiology research [7]. This online database tool provides curated information on EGRP-funded grants, peer-reviewed publications on cancer epidemiology, and genomic evidence-based recommendations. The Meta-Analysis Database, a new addendum to CGEN introduced in 2015, offers a resource for researchers to inform a research direction and identify research gaps.

The meta-analysis database facilitates assessment of the body of evidence on a particular topic related to cancer research that has been meta-analyzed while also having the ability to inquire about active funding by EGRP on a topic. The integrative features of CGEN thus provide users the resource to assess the current view of specific areas of cancer research, appreciate the nuances and gaps in research direction for a particular cancer site and/or exposure of interest and measure various factors across the basic sciences, clinical or population studies. Limitations on the utility of the CGEN Meta-Analysis Database include curation based upon publication abstracts only; perhaps, full text review may provide additional data. Furthermore, some meta-analyses may not have been captured through search algorithm, and the database does not contain meta-analyses prior to 2008.

Meta-analyses are one way to synthesize the results of previously conducted research; however, they do have methodological concerns. Not all published meta-analyses are comparable in quality as there is wide heterogeneity in the conduct of the systematic review process as well as the meta-analyses of the published findings. For example, methodological issues include the completeness of the search query, whether the reviewers adhered to rigorous search strategies to address the original scientific question of interest and what protocol was followed to meta-analyze the published results. High quality meta-analyses do follow a strict and systematic methods of inclusion or exclusion criteria and how to combine data in order to present accurate effect estimates than those attained in individual studies [12]. Therefore, meta-analyses are continually providing the scientific community with an updated and synthesized pool of literature to address research or clinical questions of interest.

It is critical to implement proper practice when conducting meta-analyses. A concise and valuable guide, 'Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)' has been created to help improve the clearness, accuracy and

comprehensiveness of systematic reviews or meta-analysis protocols of clinical trials [13]. PRISMA 2009 (for protocols) was synthesized containing a checklist of 27 items that are considered essential and necessary elements of a systematic review or meta-analysis. This guide should allow scientist to provide better transparency of their published systematic reviews and meta-analyses. Likewise, Meta-analysis Of Observational Studies in Epidemiology (MOOSE) is a valuable guide that contains checklist items for quality assessment of the meta-analyses for observational studies [14]. Moreover, peer-review of meta-analyses for publication should also maintain a rigor to ensure that the meta-analyses are properly conducted and the meta-analysis is methodologically sound.

We attempted to assess the quality of meta-analyses by selecting a random sample of 38 meta-analyses articles in our database. We assessed the quality of reporting of this selected sample against the PRISMA and MOOSE guidelines. We found variability in reporting of RCTs and observational articles (Online Resource 2), suggesting that more diligence may be needed to ensure standards of meta-analyses reporting when peer-reviewed to be published by journals.

The present paper describes a broad overview of the meta-analysis data in CGEN and shows a rapid rise in publications of meta-analyses across several areas. Our hope is that this new feature will provide users with a new resource for their knowledge integrative project or to assess the totality of the field. In-depth analyses using this data can be broad or specific to an area of interest. Furthermore, this continually updated database facilitates and provides researchers with the ability to conduct these analyses needed to continue synthesizing massive data within the field of Cancer Epidemiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Ximena V. Qadir conducted the analyses and drafted the manuscript. Mindy Clyne conducted additional data analyses and prepared the Methods section of the text. Tram Kim Lam prepared the Discussion section of the text. Muin J. Khoury drafted the Discussion section of the text and revised it for important intellectual content and contribution to the field of Epidemiology. Sheri D. Schully contributed significantly to the design of the project and supervised field activities. Significant effort and contribution was made from all authors.

References

1. Khoury MJ, Lam TK, Ioannidis JP, Hartge P, Spitz MR, Buring JE, Chanock SJ, Croyle RT, Goddard KA, Ginsburg GS, Herceg Z, Hiatt RA, Hoover RN, Hunter DJ, Kramer BS, Lauer MS, Meyerhardt JA, Olopade OI, Palmer JR, Sellers TA, Seminara D, Ransohoff DF, Rebbeck TR, Tourassi G, Winn DM, Zauber A, Schully SD. Transforming epidemiology for 21st century medicine and public health. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013; 22(4):508–516. DOI: 10.1158/1055-9965.EPI-13-0146
2. Panagiotou OA, Willer CJ, Hirschhorn JN, Ioannidis JP. The power of meta-analysis in genome-wide association studies. Annual review of genomics and human genetics. 2013; 14:441–465. DOI: 10.1146/annurev-genom-091212-153520
3. Evangelou E, Ioannidis JP. Meta-analysis methods for genome-wide association studies and beyond. Nature reviews Genetics. 2013; 14(6):379–389. DOI: 10.1038/nrg3472

4. World Cancer Research Fund-American Institute for Cancer Research Diet and Cancer Report Cancer Prevention Recommendations. [Accessed December 4 2014] <http://www.dietandcancerreport.org/>
5. Ioannidis JP, Zhou Y, Chang CQ, Schully SD, Khoury MJ, Freedman AN. Potential increased risk of cancer from commonly used medications: an umbrella review of meta-analyses. *Annals of oncology: official journal of the European Society for Medical Oncology/ESMO*. 2014; 25(1):16–23. DOI: 10.1093/annonc/mdt372
6. Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, Neumann I, Carrasco-Labra A, Agoritsas T, Hatala R, Meade MO, Wyer P, Cook DJ, Guyatt G. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA: the journal of the American Medical Association*. 2014; 312(2):171–179. DOI: 10.1001/jama.2014.5559 [PubMed: 25005654]
7. Schully SD, Rogers SD, Lam TK, Chang CQ, Clyne M, Cyr J, Watson D, Khoury MJ. The Cancer Genomics and Epidemiology Navigator: An NCI Online Tool to Enhance Cancer Epidemiology Research. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2014; 23(11):2610–2611. DOI: 10.1158/1055-9965.EPI-14-0902
8. National Library of Medicine National Center for Biotechnology Information. [Accessed October 30 2014] <http://www.ncbi.nlm.nih.gov/entrez>
9. Lin BK, Clyne M, Walsh M, Gomez O, Yu W, Gwinn M, Khoury MJ. Tracking the epidemiology of human genes in the literature: the HuGE Published Literature database. *American journal of epidemiology*. 2006; 164(1):1–4. DOI: 10.1093/aje/kwj175 [PubMed: 16641305]
10. Health NCIatNIH. A Snapshot of Breast Cancer. 2014.
11. Ioannidis JP, Chang CQ, Lam TK, Schully SD, Khoury MJ. The geometric increase in meta-analyses from China in the genomic era. *PloS one*. 2013; 8(6):e65602.doi: 10.1371/journal.pone.0065602 [PubMed: 23776510]
12. Yuan Y, Hunt RH. Systematic reviews: the good, the bad, and the ugly. *The American journal of gastroenterology*. 2009; 104(5):1086–1092. DOI: 10.1038/ajg.2009.118 [PubMed: 19417748]
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 2009; 6(7):e1000097.doi: 10.1371/journal.pmed.1000097 [PubMed: 19621072]
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama*. 2000; 283(15): 2008–2012. [PubMed: 10789670]

Fig. 1.

Search strategy and selection of cancer epidemiology meta-analysis

Note: For some codings, publications may appear in more than one group A non-parametric analysis was performed measuring trends (P_{trend}) across ordered groups (article count by year). Statistical significance was considered at $P < 0.05$. The statistical analysis was performed by Stata/SE 13 software and accessed on June 15, 2015.

Fig. 2.
Cancer meta-analysis from 2008–2013 (N=4,686)

Fig. 3.

Risk study characteristics from 2008–2013 (N=3,289) A non-parametric analysis was performed measuring trends (P_{trend}) across ordered groups (article count by year). Statistical significance was considered at $P < 0.05$. The statistical analysis was performed by Stata/SE 13 software and accessed on June 15, 2015.

Fig. 4.
Top journals with published cancer meta-analysis from 2008–2013 (N=4,686)

Fig. 5.
Cancer meta-analysis stratified by first author location (N=4,686)

Table 1

Selected Characteristics of Meta-analyses Published From 2008–2013.

Year	2008	2009	2010	2011	2012	2013	Total	p-trend
Study Type								
Observational Individual Patient Data	147	219	344	412	677	848	2647	0.030
Clinical ^a Individual Patient Data	69	107	144	171	209	221	921	0.030
Mixed Individual Patient Data	8	9	12	19	28	32	103	0.030
Not stated Individual Patient Data	61	60	100	142	276	371	1010	0.040
Total	285	395	600	744	1190	1472	4686	0.030
Cancer Care Continuum^b								
Risk	151	210	340	403	675	853	2632	0.030
Treatment	73	123	162	213	294	312	1177	0.030
Prognostic	29	34	51	70	111	224	519	0.030
Diagnostic	36	20	43	67	120	129	415	0.351
Screening	4	8	7	6	12	14	51	0.093
Total	293	395	603	759	1212	1532	4794	0.030
Cancer Sites^c								
Cancer, non-specified	37	34	58	80	142	175	526	0.040
Breast	46	44	125	126	143	172	656	0.040
Colorectal	33	53	77	90	162	176	591	0.030
Digestive	32	48	59	75	143	200	557	0.030
Lung	30	60	77	83	138	152	540	0.030

Year	2008	2009	2010	2011	2012	2013	Total	p-trend
Bladder	8	9	16	21	29	50	133	0.030
Endometrial	8	9	10	14	15	18	74	0.030
Hematologic	16	27	37	51	72	67	270	0.040
Ovarian	10	16	19	20	27	49	141	0.030
Prostate	17	27	28	38	64	83	257	0.030
Renal	4	8	10	11	11	26	70	0.032
Skin	7	10	14	17	24	23	95	0.040
Other cancer sites	65	85	107	167	282	336	1042	0.030
Total	313	430	637	793	1252	1527	4952	0.030

^aClinical can be comprised of RCTs or Non-RCTs.

^{b, c}Not mutually exclusive.