Meta Analysis – Paediatric malignancies

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Paediatric Age Group – 1-14 years upto 18-19

Malignancy	0-14 years	15-19 years
ALL	23.5%	5.6%
AML	4.7%	4.3%
CNS	22.1%	9.8%
Neuroblastoma	7.9%	
Wilm's tumour	6.0%	
NHL	5.7%	8.3%
Hodgkin's	3.6%	16.8%
RMS, Retinoblastoma	3.6%	
Non RMS Soft tissue sarcoma	5.1%	5.1%
GCT	3.5%	12.4%
Melanoma		7.6%
Thyroid		7.3%
Osteosarcoma		4.2%
Ewing's sarcoma		2.4%

Principles and Practice of Paediatric Oncology, 4th Edn

Search Engines

Meta-analysis is a statistical method used to provide a single summary risk estimate based on a set of similar epidemiological studies

Heterogeneity due to design differences among studies in exposure assessment, confounder assessment, subject selection, quality, bias, accuracy, uncertainties

- PubMed, Scopus
- Google scholar
- ISI web of science
- WHO Global Health Library
- POPLINE, VHL, NYAM – New York Academy of Medicine
- SIGLE – System for Information on Grey Literature in Europe
- MEDLINE, EMBASE, CINAHL
- Electronic databases in the Cochrane Controlled Trials Register

- Not many meta analysis on clinical presentation or treatment
- Many are **Epidemiological studies**

Some Terminologies

- MOOSE – Meta analysis Of Observational Studies in Epidemiology
- 9 Star- New Castle – Ottawa Scale (NOS) – Quality of the study – for non-randomized studies
- PRISMA – Preferred Reporting Items for Systemic reviews and Meta Analysis
- STROBE – Strengthening The Reporting Of Observational studies in Epidemiology – for cohort studies
- CASP – Critical Appraisal Skills Programme – for case-control and cohort studies
- QUADAS – Quality Assessment of Diagnostic Accuracy Studies
- QUOROM – Quality of Reporting Meta-analysis

Statistics

- Meta Regression Method
- Q and I^2 statistics
- Bias – Funnel Plot
- Quantitative Exam of bias – Begg's rank correlation test, Egger's rank correlation test, Kendall's rank correlation co-efficient (Kendall's tau)

The Cochrane Collaboration Tool has 6 domains –

→ sequence generation
→ allocation concealment
→ blinding of participants and personnel
→ incomplete outcome data
→ selective outcome reporting
→ other sources of bias

- Comprehensive Meta analysis
- Harvard test for small study effects (binary outcome data)

Exposure to pesticides and risk of childhood cancer: recent epidemiological studies

Two cohort and 38 case-control studies

Results: Three cohort studies did not show any positive links between parental pesticide exposure and childhood cancer incidence.

40 studies with OR values showed that the risk of lymphoma and leukaemia increased significantly in exposed children when their mother was exposed during the prenatal period (OR¼1.53; 95% CI 1.22 to 1.91 and OR¼1.48; 95% CI 1.26 to 1.75).

The risk of brain cancer was correlated with paternal exposure either before or after birth (OR¼1.49; 95% CI 1.23 to 1.79 and OR¼1.66; 95% CI 1.11 to 2.49).

Conclusion: Despite some limitations in this study, the incidence of childhood cancer does appear to be associated with parental exposure during the prenatal period

Occup Environ Med 2011;68:694e702.

Meta-Analysis in Leukemias

1. Early Vaccination Protects Against Childhood Leukemia
2. Association between Childhood Infections & the Risk of Childhood Acute Lymphoblastic Leukemia
3. Residential Magnetic Fields and Childhood Leukemia
4. Clinical Presentation of Childhood Leukemia
5. Thrombotic Complications in Childhood ALL
6. Chemotherapy only Treatment Effects on long-term Neurocognitive Functioning in Childhood ALL Survivors
7. Obesity in Paediatrics Acute Lymphoblastic Leukemia Survivors
8. Gene Expression in Relapsed Childhood B-Acute Lymphoblastic Leukemia

Summary of Meta-Analysis in Leukemias

1. Early Vaccination Protects Against Childhood Leukemia – ***Early vaccination with BCG may be protective***
2. Association between Childhood Infections & the Risk of Childhood Acute Lymphoblastic Leukemia – ***No Association***
3. Residential Magnetic Fields and Childhood Leukemia - ***somewhat weak elevated risk of leukemia for children living in proximity to power lines***
4. Clinical Presentation of Childhood Leukemia - ***95 presenting symptoms and sign out of which 5 features present in >50% of children***

Summary of Meta-Analysis in Leukemias

5. Thrombotic Complications in Childhood ALL – ***higher***
6. Chemotherapy only Treatment Effects on long-term Neurocognitive Functioning in Childhood ALL Survivors - ***significant IQ deficits of 6 to 8 points***
7. Obesity in Paediatrics Acute Lymphoblastic Leukemia Survivors - ***Obesity is prevalent in pediatric ALL survivors***
8. Gene Expression in Relapsed Childhood B-Acute Lymphoblastic Leukemia - ***S100A8 is the most overexpressed gene and a promising biomarker***

Risk Factors of Childhood Lymphoma

- Genetic aberrations promoting proliferation, differentiation and apoptosis
- Epstein-Barr virus infection
- Socioeconomic status
- Environmental stimuli
- Genetic predisposition
- Immunodeficiency disorders
- Maternal smoking

Meta-Analysis in Lymphomas

1. Is Birth Weight Associated with Childhood Lymphoma?
2. Breast Feeding and the Risk of Childhood Hodgkin Lymphoma
3. Chemotherapy vs Combined Modality Treatment Trials in Hodgkin's disease
4. Second Malignancy Risk Associated with Treatment of Hodgkin's lymphoma
5. Prevalence of Hepatitis C Infection in B cell NHL
6. Risk of Second Malignancies in non-Hodgkin's Lymphoma Survivors

Summary of Meta-Analysis in Lymphomas

1. Is Birth Weight Associated with Childhood Lymphoma? - ***non statistically significant positive association of high birth weight with childhood NHL***

2. Breast Feeding and the Risk of Childhood Hodgkin Lymphoma - ***Limited evidence for a significant association between breastfeeding and the risk of childhood Hodgkin Lymphoma***

3. Chemotherapy vs Combined Modality Treatment Trials in Hodgkin's disease - ***clear benefit for RT – 11% complete remission at 10 years***

Summary of Meta-Analysis in Lymphomas

4. Second Malignancy Risk Associated with Treatment of Hodgkin's lymphoma - ***Administration of RT and CT marginally increases overall SMR in advanced stages. Breast cancer risk (but not SMR in general) was substantially higher after EF-RT.***
5. Prevalence of Hepatitis C Infection in B cell NHL - ***HCV prevalence in patients with B-NHL is~15% higher than general population***
6. Risk of Second Malignancies in non-Hodgkin's Lymphoma Survivors - ***higher risk of SMNs than the general population and stressed the possible carcinogenic effect of chemotherapy and combined modality therapy***

SMN/SMR- Second Malignancy; CT – Chemotherapy, EFRT –Extended Field RT

Meta-Analysis in Brain Tumours

1. Parental Smoking and the Risk of Childhood Brain Tumours
2. Arterial Spin Labeling in Children with Brain Tumour
3. Presentation of Childhood CNS tumours
4. Molecular subgroups of Medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations
5. Survival and Prognostic Factors of Early Childhood Medulloblastma
6. Integrated Molecular Meta-Analysis of 1000 Paediatric High Grade and Diffuse Intrinsic Pontine Glioma
7. Survival Rates and Prognostic Outcomes of High Grade Brain Stem Gliomas in Childhood
8. Neurocognitive Consequences of a Paediatric Brain Tumour and its Treatment
9. Neurocognitive Sequelae in Survivors of Paediatric Brain Tumours

Summary of Meta-Analysis in Brain Tumours

1. Parental Smoking and the Risk of Childhood Brain Tumours – ***No Association***
2. 2. Arterial Spin Labeling in Children with Brain Tumour - ***high diagnostic accuracy to discriminate low and high grade tumours***

3. Presentation of Childhood CNS tumours - ***56 symptoms and signs at diagnosis***
4. Molecular subgroups of Medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations - ***four core molecular subgroups of medulloblastoma are found*** across all published datasets
5. Survival and Prognostic Factors of Early Childhood Medulloblastma - ***desmoplastic variants of medulloblastomas in early childhood and histopathology as a strong independent prognostic factor.***

Summary of Meta-Analysis in Brain Tumours

6. Integrated Molecular Meta-Analysis of 1000 Paediatric High Grade and Diffuse Intrinsic Pontine Glioma - ***Genomic aberrations increase with age, highlighting the infant population as biologically and clinically distinct***
7. Survival Rates and Prognostic Outcomes of High Grade Brain Stem Gliomas in Childhood – ***very poor***
8. Neurocognitive Consequences of a Paediatric Brain Tumour and its Treatment
9. Neurocognitive Sequelae in Survivors of Paediatric Brain Tumours – ***both meta-analysis show significant declines in both broad and specific domains of neurocognitive functioning.***

Parental Occupation and Ewing's sarcoma: Pooled and meta-analysis

- 3 case-control studies to assess the overall associations between parental occupation and ESFT. 199 cases and 1,451 controls.
- The pooled odds ratio for the periconception and gestation periods were 2.3 (95% CI = 1.3–4.1) for children whose fathers had worked on farms and 3.9 (95% CI = 1.6–9.9) for those whose mothers had farmed. For the periconception and gestation periods, there was a 3.5-fold increased risk for those with both parents having farmed.
- Provides evidence supporting the hypothesis of an association between ESFT and parental occupation in farming.

Int J Cancer2005; 115:799-806

Prognostic Significance of serum Lactate Dehydrogenase levels in Ewing's sarcoma

- Nine cohort studies, between 1980 and 2014, n= 1,412 patients
- Six studies, with a total of 644 patients, used OS as the primary endpoint and four studies, with 795 patients, used 5-year DFS.
- Overall, the pooled HR evaluating high LDH levels was 2.90 (95% CI: 2.09-4.04) for OS and 2.40 (95% CI: 1.93-2.98) for 5-year DFS.
- This meta-analysis demonstrates that high levels of serum LDH are associated with lower OS and 5-year DFS rates in patients with Ewing's sarcoma.
- Therefore, serum LDH levels are an **effective biomarker** of Ewing's sarcoma prognosis

Molecular and Clinical Oncology 2016;5:832-38

Meta-Analysis in Osteosarcoma

1. MDM2 Polymorphisms in Osteosarcoma susceptibility
2. Osteosarcoma: A Meta-Analysis and Review of the Literature
3. Does intensified chemotherapy increase survival outcomes of Osteosarcoma patients?
4. Prognostic value of microRNAs in Osteosarcoma
5. Osteosarcoma Outcomes in the Modern Medical Era

Summary of Meta-Analysis in Osteosarcoma

1. MDM2 Polymorphisms in Osteosarcoma susceptibility - ***MDM2 rs1690916 and rs2279744 cannot be considered as genetic risk factors for OS susceptibility in the different populations.***

2. Osteosarcoma: A Meta-Analysis and Review of the Literature - ***Tumour necrosis is an important predictor of patient prognosis. Fifty percent of the patients with non- metastatic osteosarcoma achieved 90% necrosis on histology.***

3. Does intensified chemotherapy increase survival outcomes of Osteosarcoma patients? - ***no significant differences between intensified and conventional chemotherapy***

4. Prognostic value of microRNAs in Osteosarcoma - ***Expression level of miRNA in patients of osteosarcoma is important as a prognostic factor.***

5. Osteosarcoma Outcomes in the Modern Medical Era - ***no improvement in published osteosarcoma survival has been seen since 1980***

Efficacy Comparison of Six Chemotherapeutic Combinations for Osteosarcoma and Ewing's Sarcoma Treatment

- 787 studies – 28 studied selected (n=5628) of which 18 were RCTs
- All chemo drugs and combinations extended patient's life span and multi-drug with IFO and Etoposide being the optimal choice
- Multidrug with IFO alone was the most efficient in preventing relapse and lung metastases.
  (IFO -Ifosfamide and Etoposide)

J of Cellular Biochemistry 2018;119:250-59

Meta-Analysis in Neuroblastoma

1. Birth Weight and Risk of Neuroblastoma: a Meta-Analysis
2. Maternal Smoking during Pregnancy and Risk of Childhood Neuroblastoma
3. ^{123}I-Meta-Iodobenzylguanidine Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma
4. Neuroblastoma reveals a Skewed ALK Mutation Spectrum in Tumors with MYCN Amplication
5. Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials

Summary of Meta-Analysis in Neuroblastoma

1. Birth Weight and Risk of Neuroblastoma: a Meta-Analysis - ***High birth weight is highly reproducibly associated with increased risk of neuroblastoma.***

2. Maternal Smoking during Pregnancy and Risk of Childhood Neuroblastoma - ***possible association between maternal smoking during pregnancy and pediatric Neuroblastoma development.***

3. ^{123}I-Meta-Iodobenzylguanidine Scintigraphy for the Detection of Neuroblastoma and Pheochromocytoma - ***^{123}I-mIBG scintigraphy has sensitivity and specificity greater than 90% for detection of neuroblastoma and pheochromocytoma.***

Summary of Meta-Analysis in Neuroblastoma

4. Neuroblastoma reveals a Skewed ALK Mutation Spectrum in Tumors with MYCN Amplication - ***F1174 hotspot mutations are associated with MYCN amplification and their combined occurrence leads to fatal disease outcome***

5. Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials - ***this study provides baseline data on clinical out- come variables for children with relapsed and refractory neurob- lastoma that will help the design of future clinical trials as well as provide parents and patients with most accurate information about outcomes.***

Meta-Analysis in Wilms' Tumour

1. Wilms' tumour: a systematic review of risk factors and meta-analysis
2. Genetic variation frequencies in Wilms' tumor: A meta-analysis and systematic review
3. Loss of heterozygosity on chromosome 16q increases relapse risk in Wilms' tumor: a meta-analysis
4. Tumor Risk in Beckwith–Wiedemann Syndrome: A Review and Meta-Analysis
5. Wilms' tumor 1 (WT1) expression and prognosis in solid cancer patients: a systematic review and meta-analysis

Summary of Meta-Analysis in Wilms' Tumou

1. Wilms' tumour: a systematic review of risk factors and meta-analysis

   Decreased risk of Wilms' tumour was observed ***for second or later births compared with a first child***

   Increased risk of Wilms' tumour with
   - ***maternal exposure to pesticides prior to the child's birth***
   - ***high birthweight***
   - ***preterm birth***
   - ***Maternal hypertension***

2. Genetic variation frequencies in Wilms' tumor: A meta-analysis and systematic review - Gene mutations WT1, WTX, CTNNB1, TP53, MYCN, DROSHA, and DGCR8 - ***no study-level characteristics of indicators were found***

Summary of Meta-Analysis in Wilms' Tumour

3. Loss of heterozygosity on chromosome 16q increases relapse risk in Wilms' tumor: a meta-analysis - ***LOH 16q was more effective on elevated replase risk in patients with favorable- histology WT***

4. Tumor Risk in Beckwith–Wiedemann Syndrome: A Review and Meta-Analysis - ***strong association between a LOI of H19 and especially Wilms tumor development in BWS.***

5. Wilms' tumor 1 (WT1) expression and prognosis in solid cancer patients: a systematic review and meta-analysis - ***WT1 may be a potential marker to predict DFS/RFS/PFS in solid tumor patients***

Childhood infections, Orchitis and Testicular Germ Cell Tumour: Report from the STEED Study

To evaluate the relationship between common infections occurring during childhood or young adult life and TGCT using existing data from the US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) case–control study.

TGCT cases diagnosed between 2002 and 2005 (n¼767) were matched on age, race and serum draw date to at least one control (n¼929).

RESULTS: None of the infections evaluated were associated with TGCT risk. Mumps pooled odds ratio (OR): 1.03, 95% CI: 0.89–1.20; mumps orchitis or orchitis pooled OR: 1.80, 95% CI: 0.74–4.42.

CONCLUSION: TGCT does not appear to be associated with common childhood infections.

Bristish J of Cancer 2012;106:1331-34

Summary

- It is highly desirable for a meta-analysis to include a sensitivity analysis to determine the "robustness" of the results.
  - Two common ways to perform sensitivity analysis are to analyze the data using various methods and to present the results when some studies are removed from the analysis.
  - If these actions cause serious changes in the overall results, the credibility of the results is compromised.
- The strength of meta-analysis is that, by pooling many studies, the effective sample size is greatly increased, and consequently more variables and outcomes can be examined.
  - For example, analysis in subsets of patients and regression analyses that could not be done in individual trials can be performed in a meta-analysis.

Conclusion

Even small violations of the rules of meta-analysis can lead to misleading results.

Exclusion of nonpublished studies increases selection bias.

'Data-mining' greatly increases the risk of false- positive results.

With rare effects,even a small difference can seem large.

Randomized trials are the gold standard, but meta- analyses provide valuable complementary information.

- Many are **Epidemiological studies**
- Very few studies on clinical presentation, treatment
- These meta-analysis is a platform for further research