TECHNICAL COMMENTARY

Cancer

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Introduction

Cancer is a broad group of diseases involving abnormal cell growth such that cells divide and grow forming malignant tumours that may spread through the lymphatic system or blood stream. Not all tumours are malignant – some remain benign and do not invade other organs. Lifestyle, genetic factors and environmental pollutants increase a persons' risk of developing cancer. Cancer can affect people of all ages. The most common cancers include lung cancer (22% of all cancers), bowel cancer (12%), breast cancer (8-23%) and prostate cancer (7%). Cancer may be measured by incidence or mortality rates: incidence refers to how many new cases there are in a population, while mortality refers to the rate of deaths due to cancer in a specific population.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data were prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having < 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate, or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight systematic reviews that met our inclusion criteria[3-10].

Multiple reviews assessed the same cancers and found conflicting results for breast, liver, lung and colorectal cancers. This is due to

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

differences in inclusion criteria and differences in the way analyses were conducted.

- Moderate to high quality evidence suggests a small increase in rates of breast cancer in women with schizophrenia, a small decrease in rates of prostate cancer in men with schizophrenia, and a small decrease in rates of malignant melanoma in people with schizophrenia. This review found no differences in rates of brain, colorectal or lung cancers.
- Moderate to high quality evidence finds a small decrease in any cancer in people with schizophrenia, although there were no differences when males and females were assessed separately. The rates of prostate and colorectal cancers were reduced in men (small to medium effects), and lung cancer may be increased in women (small effect). This review found no differences in rates of breast, liver or stomach cancers.
- Moderate to high quality evidence suggests a decreased incidence of liver cancer prior to a diagnosis of schizophrenia, and an increased incidence of liver cancer after a diagnosis of schizophrenia in males but not females.
- Moderate to high quality evidence suggests an increased incidence of breast cancer in women, particularly when breast cancer occurred after a diagnosis of schizophrenia.
- Moderate to high quality evidence suggests cancer-related mortality in people with schizophrenia is increased by about 40% compared to general population rates.
- High quality evidence suggests a small decreased incidence of any cancer in parents and siblings of people with schizophrenia.

Catalá-López F, Suárez-Pinilla M, Suárez-Pinilla P, María Valderas J, Gómez-Beneyto M, Martinez S, Balanzá-Martínez V, Climent J, Valencia A, McGrath J, Crespo-Facorro B, Sanchez-Moreno J, Vieta E, Tabarés-Seisdedos R

Inverse and Direct Cancer Comorbidity in People with Central Nervous System Disorders: A Meta-Analysis of Cancer Incidence in 577,013 Participants of 50 Observational Studies

Psychotherapy and Psychosomatics 2014; 83: 89-105

View review abstract online

Comparison	**Rates cancer in people with schizophrenia vs. people without schizophrenia. This review included prospective cohort studies and/or nested case-control studies.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) suggests a small increase in rates of breast cancer in women with schizophrenia, and a medium-sized decrease in rates of prostate cancer in men with schizophrenia. There is also a small decrease in rates of malignant melanoma in men or women with schizophrenia. There were no significant differences in brain, colorectal or lung cancers.**

Incidence of any cancer

16 studies, N = 427,843

Any cancer

No significant differences in incidence rates;

16 studies, ES = 0.98, 95%CI 0.90 to 1.07, $p > 0.05$, $I^2 = 96\%$, $p < 0.01$

Breast cancer

Small increased incidence in women with schizophrenia;

15 studies, ES = 1.25, 95%CI 1.10 to 1.42, $p < 0.05$, $I^2 = 90\%$, $p < 0.01$

Prostate cancer

Small to medium decreased incidence in men with schizophrenia;

12 studies, ES = 0.55, 95%CI 0.45 to 0.67, $p < 0.05$, $I^2 = 60\%$, $p < 0.01$

Malignant melanoma

Small decreased incidence in people with schizophrenia;

5 studies, ES = 0.72, 95%CI 0.62 to 0.83, $p < 0.05$, $I^2 = 0.6\%$, $p = 0.40$ Brain cancer *No significant differences in incidence rates;* 8 studies, ES = 1.00, 95%CI 0.76 to 1.31, $p > 0.05$, $I^2 = 78\%$ Colorectal cancer *No significant differences in incidence rates;* 12 studies, ES = 0.95, 95%CI 0.80 to 1.13, $p > 0.05$, $I^2 = 87\%$ Lung cancer *No significant differences in incidence rates;* 14 studies, ES = 0.92, 95%CI, 0.72 to 1.17, $p > 0.05$, $I^2 = 95\%$

Consistency in results‡	Inconsistent, apart from malignant melanoma.
Precision in results§	Precise
Directness of results‖	Direct

Catts VS, Catts SV, O'Toole BI, Frost ADJ

Cancer incidence in patients with schizophrenia and their first degree relatives - a meta-analysis

Acta Psychiatrica Scandinavica 2008; 117: 323-336

View review abstract online

Comparison	**Incidence of cancer in first-degree relatives of people with schizophrenia vs. general population. This review included population, register-based studies.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests decreased incidence of any cancer in parents and siblings of people with schizophrenia.**
Incidence of any cancer	
Small decreased incidence in first-degree relatives; Parents: 3 studies, N = 70,484, SIR = 0.90, 95%CI 0.88 to 0.93, $p < 0.00001$, Q p not significant Siblings: 2 studies, N = 72,267, SIR = 0.89, 95%CI 0.84 to 0.94, $p < 0.0001$, Q p not significant	

Consistency	Consistent
Precision	Appears precise
Directness	Direct

Li H, Li J, Yu X, Zheng H, Sun X, Lu Y, Zhang Y, Li C, Bi X

The incidence rate of cancer in patients with schizophrenia: A meta-analysis of cohort studies

Schizophrenia Research 2018; 195: 519-28

View review abstract online

Comparison	**Incidence of cancer in people with schizophrenia vs. general population. This review included population-based retrospective and prospective cohort studies.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, mostly precise, direct) finds a small decrease in any cancer in people with schizophrenia, although there were no differences when males and females were assessed separately. The rates of prostate and colorectal cancers were reduced in men (small to medium effects), and lung cancer was increased in women (small effect). There were no significant differences in rates of breast, liver or stomach cancers.**

Incidence of any cancer

16 studies, N > 545,608

Any cancer

Small, decreased incidence in people with schizophrenia;

13 studies, RR = 0.90, 95%CI 0.81 to 0.99, $p = 0.04$, $I^2 = 75\%$

No significant differences in the subgroup analyses of males and females separately;

Males: 8 studies, RR = 0.86, 95%CI 0.72 to 1.03, $p = 0.11$, $I^2 = 98\%$

Females: 8 studies, RR = 1.03, 95%CI 0.94 to 1.14, $p = 0.50$, $I^2 = 94\%$

Prostate cancer

Small to medium decreased incidence in men with schizophrenia;

10 studies, RR = 0.55, 95%CI 0.42 to 0.71, $p < 0.00001$, $I^2 = 85\%$ Colorectal cancer *Small decreased incidence in people with schizophrenia;* 8 studies, RR = 0.82, 95%CI 0.69 to 0.98, $p = 0.03$, $I^2 = 74\%$ *Small decreased incidence in males but not females;* Males: 4 studies, RR = 0.89, 95%CI 0.81 to 0.98, $p = 0.02$, $I^2 = 0\%$ Females: 4 studies, RR = 0.99, 95%CI 0.92 to 1.07, $p = 0.80$, $I^2 = 0\%$ Lung cancer *No significant differences in incidence rates;* 9 studies, RR = 1.01, 95%CI 0.76 to 1.35, $p = 0.92$, $I^2 = 91\%$ *Small increased incidence in females but not males;* Females: 5 studies, RR = 1.12, 95%CI 1.01 to 1.25, $p = 0.04$, $I^2 = 11\%$ Males: 6 studies, RR = 1.06, 95%CI 0.90 to 1.25, $p = 0.51$, $I^2 = 73\%$ Breast cancer *No significant differences in incidence rates;* 12 studies, RR = 1.08, 95%CI 0.93 to 1.25, $p = 0.31$, $I^2 = 92\%$ Liver cancer *No significant differences in incidence rates;* 5 studies, RR = 0.89, 95%CI 0.57 to 1.41, $p = 0.63$, $I^2 = 84\%$ Males: 3 studies, RR = 0.99, 95%CI 0.84 to 1.16, $p = 0.87$, $I^2 = 0\%$ Females: 3 studies, RR = 1.07, 95%CI 0.70 to 1.66, $p = 0.75$, $I^2 = 61\%$ Stomach cancer *No significant differences in incidence rates;* 6 studies, RR = 0.77, 95%CI 0.57 to 1.04, $p = 0.09$, $I^2 = 72\%$ Males: 4 studies, RR = 0.89, 95%CI 0.77 to 1.03, $p = 0.12$, $I^2 = 0\%$ Females: 4 studies, RR = 0.95, 95%CI 0.78 to 1.16, $p = 0.62$, $I^2 = 14\%$	
Consistency	Mostly inconsistent
Precision	Mostly precise
Directness	Direct

Xiping Z, Shuai Z, Feijiang Y, Bo C, Shifeng Y, Qihui C

Meta-analysis of the Correlation Between Schizophrenia and Breast Cancer

Clinical Breast Cancer 2019; 19: e172-e85

View review abstract online

Comparison	**Incidence of breast cancer in people with schizophrenia vs. general population or controls without schizophrenia. This review included retrospective and prospective studies.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests an increased rate of breast cancer in females but not males with schizophrenia.**
Incidence of breast cancer	
Small increased incidence in people with schizophrenia; 15 studies, N = RR = 1.18, 95%CI 1.05 to 1.32, $p < 0.05$, $I^2 = 89\%$ Subgroup analysis of gender showed the effect was significant only for females. Subgroup analysis of geographic region showed the effect was significant for studies conducted in Europe, but not for Asian studies.	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Xu D, Chen G, Kong L, Zhang W, Hu L, Chen C, Li J, Zhuo C

Lower risk of liver cancer in patients with schizophrenia: A systematic review and meta-analysis of cohort studies

Oncotarget 2017; 8: 102328-35

View review abstract online

Comparison	**Incidence of liver cancer in people with schizophrenia vs. general population. This review included retrospective and prospective cohort studies.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent,**

	precise, direct) suggests a decreased incidence of liver cancer prior to a diagnosis of schizophrenia, and an increased incidence of liver cancer after a diagnosis of schizophrenia in males but not females.
Incidence of liver cancer	
7 studies, N = 312,834 *No significant differences in incidence rates;* SIR = 0.83, 95%CI 0.66 to 1.04, p = 0.10, I^2 = 81% *Subgroup analysis of patients with cancer events before a diagnosis of schizophrenia showed a small effect of decreased incidence of liver cancer;* 5 studies, SIR = 0.76, 95%CI 0.61 to 0.96, p = 0.02, I^2 = 84% *Subgroup analysis excluding patients with cancer events before a diagnosis of schizophrenia showed a small effect of higher incidence of liver cancer in males, but not females;* Males: 5 studies, SIR = 0.71, 95%CI 0.56 to 0.90, p = 0.005, I^2 = 79% Females: 5 studies, SIR = 0.83, 95%CI 0.65 to 1.05, p = 0.12, I^2 = 63%	
Consistency	Inconsistent
Precision	Appears precise
Directness	Direct

Zhuo C, Triplett PT

Association of schizophrenia with the risk of breast cancer incidence a meta-analysis

JAMA Psychiatry 2018; 75: 363-9

View review abstract online

Comparison	**Incidence of breast cancer in women with schizophrenia vs. general population. This review included retrospective and prospective cohort studies.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests an increased incidence of breast cancer in women, particularly in large studies and in those where breast cancer occurred after a diagnosis of**

	schizophrenia.
Incidence of breast cancer	
Small increased incidence in women with schizophrenia; 12 studies, N = 125,760, SIR = 1.31, 95%CI 1.14 to 1.50, $p < 0.001$, $I^2 = 89\%$ This effect remained after excluding studies where breast cancer occurred before the diagnosis of schizophrenia and in studies with more than 100 breast cancer cases, but not in studies that did not specify the exclusion of breast cancer cases before the diagnosis of schizophrenia, or in studies with fewer than 100 breast cancer cases (low power).	
Consistency	Inconsistent
Precision	Appears precise
Directness	Direct

Zhuo C, Tao R, Jiang R, Lin X, Shao M

Cancer mortality in patients with schizophrenia: systematic review and meta-analysis

British Journal of Psychiatry 2017; 211: 7-13

View review abstract online

Comparison	**Rate of cancer-related mortality in people with schizophrenia vs. the general population. Most studies were population-based register studies.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests around 40% increased cancer-related mortality in people with schizophrenia.**
Cancer-related mortality	
Around 40% increased cancer-related mortality in people with schizophrenia; 15 studies, N > 1,254,160, SMR = 1.39, 95%CI 1.28 to 1.52, $p < 0.001$, $I^2 = 95\%$ Subgroup analysis of gender found similar effect sizes for males and females.	
Consistency	Inconsistent

Cancer

Precision	Appears precise
Directness	Direct

Zhuo C, Zhuang H, Gao X, Triplett PT

Lung cancer incidence in patients with schizophrenia: meta-analysis.

British Journal of Psychiatry 2019; 215: 704-11

View review abstract online

Comparison	**Incidence of lung cancer in people with schizophrenia vs. general population. This review included retrospective and prospective studies.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests no difference in the rate of lung cancer.**
Incidence of lung cancer	
No significant difference between groups; 12 studies, N = 496,265, SIR = 1.11, 95%CI 0.90 to 1.37, p = 0.31, I^2 = 94% Subgroup analysis found similar results in males and females.	
Consistency	Inconsistent
Precision	Appears precise
Directness	Direct

Explanation of acronyms

CI = confidence interval, ES = effect size, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, SIR = standardised incidence ratio, SMR = standardised mortality rate, RR = risk ratio, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[11].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[11].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[11];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[13].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Catts VS, Catts SV, O'Toole BI, Frost AD, Frost ADJ (2008): Cancer incidence in patients with schizophrenia and their first-degree relatives - a meta-analysis. *Acta Psychiatrica Scandinavica* 117: 323-36.
4. Catala-Lopez F, Suarez-Pinilla M, Suarez-Pinilla P, Valderas JM, Gomez-Beneyto M, Martinez S*, et al.* (2014): Inverse and direct cancer comorbidity in people with central nervous system disorders: A meta-analysis of cancer incidence in 577,013 participants of 50 observational studies. *Psychotherapy and Psychosomatics* 83: 89-105.
5. Li H, Li J, Yu X, Zheng H, Sun X, Lu Y*, et al.* (2018): The incidence rate of cancer in patients with schizophrenia: A meta-analysis of cohort studies. *Schizophrenia Research* 195: 519-28.
6. Xu D, Chen G, Kong L, Zhang W, Hu L, Chen C*, et al.* (2017): Lower risk of liver cancer in patients with schizophrenia: A systematic review and meta-analysis of cohort studies. *Oncotarget* 8: 102328-35.
7. Zhuo C, Tao R, Jiang R, Lin X, Shao M (2017): Cancer mortality in patients with schizophrenia: systematic review and meta-analysis. *British Journal of Psychiatry* 211: 7-13.
8. Zhuo C, Triplett PT (2018): Association of schizophrenia with the risk of breast cancer incidence a meta-analysis. *JAMA Psychiatry* 75: 363-9.
9. Xiping Z, Shuai Z, Feijiang Y, Bo C, Shifeng Y, Qihui C (2019): Meta-analysis of the Correlation Between Schizophrenia and Breast Cancer. *Clinical Breast Cancer* 19: e172-e85.
10. Zhuo C, Zhuang H, Gao X, Triplett PT (2019): Lung cancer incidence in patients with schizophrenia: meta-analysis. *British Journal of Psychiatry* 215: 704-11.
11. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
12. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
13. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*