Wróblewski Hubert, Chojęta Dariusz, Zimna Aleksandra, Zygmunt Ewelina, Wróblewska Kinga. Is schizophrenia just a mental illness? - The correlation between schizophrenia and cancer. Journal of Education, Health and Sport. 2022;12(5):184-192. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.05.013 https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.05.013 https://zenodo.org/record/6568649

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 1, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences) and Health Sciences); Health Sciences (Field of Medical Sciences) and Health Sciences); Health Sciences (Field of Medical Sciences) and Health Sciences); Health Sciences (Field of Medical Sciences);

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 1 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

© The Authors 2022; This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons.org/licenses/by-nc-sa/4.00) which permits unrestricted, non commercial use, distribution and reproduction in any medium, (http://creativecommons.org/licenses/by-nc-sa/4.00) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited. The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.05.2022. Revised: 20.05.2022. Accepted: 20.05.2022.

Is schizophrenia just a mental illness? - The correlation between schizophrenia and cancer

Chojęta, Hubert Wróblewski, Dariusz Aleksandra Zimna, Ewelina Zygmunt, Kinga Wróblewska

Faculty of Medicine, Medical University of Lublin

ORCID ID and email:

Hubert Wróblewski https://orcid.org/0000-0002-1666-1650; hwwroblewski@gmail.com Dariusz Chojeta https://orcid.org/0000-0002-6474-854X; dariusz.chojeta@gmail.com Aleksandra Zimna https://orcid.org/0000-0002-8712-3497; aleksandra zimna97@wp.pl Ewelina Zygmunt https://orcid.org/0000-0002-3724-2164; ewelinazygmunt26@gmail.com Kinga Wróblewska https://orcid.org/0000-0002-8740-9401; kinga.wroblewska.kw@gmail.com

Abstract

Introduction and purpose of the work: Schizophrenia is a mental illness that affects approximately 24 million people worldwide. It is characterized by hallucinations, most often auditory, delusions, blunted affect, and distortions of thought, such as echoes of thought and perception. There is a predisposition to more frequent diabetes, metabolic syndrome, hormonal disorders, cardiovascular diseases and respiratory diseases, even in patients not treated with antipsychotics. In connection with the above, the question may arise whether schizophrenia also predisposes to developing other diseases, such as cancer. The aim of this article is to present the relationship between the occurrence of schizophrenia and cancer.

State of knowledge: There was no correlation between an increased incidence of lung cancer and schizophrenia, however, the analyzed studies were not homogeneous. In the case of breast cancer, data suggest a higher incidence of breast cancer among people with psychiatric disorders. In prostate cancer, a lower risk of developing the disease has been reported in patients with schizophrenia. It should be noted that despite the predisposition of people with schizophrenia to addiction to stimulants, low physical activity, the increase in the risk of cancer in some studies was not very high.

Summary: It can be noticed that there is a correlation between the occurrence of schizophrenia and the predisposition to developing malignant neoplasms. Currently, hope is placed on their use in anti-cancer therapy.

Key words: schizophrenia; cancer; risk of getting sick

Introduction and purpose of the work

Schizophrenia is a mental illness that affects approximately 24 million people worldwide[1]. The risk factors for developing schizophrenia include genetic susceptibility as well as environmental factors, such as: pregnancy and postpartum complications, growing up in an urban environment, migration, childhood trauma or substance abuse [2]. According to the ICD-10, it is characterized by the presence of auditory hallucinations, the occurrence of delusions, blunted affect and distortions of thinking, such as, for example, echoes of thoughts and perceptions. Schizophrenia may be continuous or episodic, with remissions[3]. Although it is not one of the most common mental problems, it is associated with significant suffering for people who suffer from it. The risk of suicide is also associated with the occurrence of schizophrenia, which is estimated at about 4%, but it should be emphasized that earlier analyzes estimated it at 10% [4]. In addition to the already mentioned mental symptoms, patients suffering from schizophrenia are also accompanied by somatic problems. There is a predisposition to more frequent diabetes, metabolic syndrome, hormonal disorders, cardiovascular diseases and respiratory diseases, even in patients not treated with antipsychotics. In addition, patients often lead a less active lifestyle and are addicted to nicotine, alcohol or other psychoactive substances [5]. The result is, inter alia, shorter life expectancy compared to the general population, by up to 25 years [6, 7]. It should be emphasized that in the course of schizophrenia, there is a disturbance and interaction of the pathway of neurotransmitters, inflammatory and endothelial mechanisms, which suggests treating schizophrenia as a systemic disease [6]. In connection with the above, the question arises whether schizophrenia also predisposes to developing other diseases, such as cancer. There are reports on the relationship between the incidence of schizophrenia and cancer incidence and their slightly different course compared to the healthy population. The aim of this article is to present the relationship between the occurrence of schizophrenia and cancer. The relationship is somewhat different for individual tumors. Therefore, in the article we present data on the most common neoplasms or those most proven to be associated with the occurrence of schizophrenia.

State of knowledge

So far, a number of studies have been carried out to show a possible correlation between the incidence of schizophrenia and cancer. One of the meta-analyzes presented the general risk of developing cancer among patients with schizophrenia. Based on 16 cohort studies from different countries, a slight decrease in the overall cancer incidence rate was demonstrated (RR = 0.90, 95% CI 0.81– 0.99)[8] in turn, two Scandinavian studies showed an increased risk of malignant neoplasm in this group of people; *Momen et al.* showed RR = 1.05 (1.03– 1.08)(9-12).

As is well known, lung cancer is one of the most common malignant neoplasms. *Zhuo et al.*, in their updated meta-analysis of 12 cohorts, found no association between an increased incidence of lung cancer and schizophrenia, but the analyzed studies were not homogeneous. Similar data were obtained for both men and women[13]. However, it is worth remembering that up to 60% of people suffering from schizophrenia are tobacco smokers [14]. Therefore, it is necessary to take a closer look at reports presenting schizophrenia as a protective factor in the incidence of certain cancers. This may also be supported by slightly older studies, when after adjusting for smoking, the risk of developing the disease turned out to be lower [15]. On the other hand, a French study comparing 633 patients with schizophrenia with a control group showed that the survival was 6 years shorter and the time from diagnosis to death. In addition, people with schizophrenia required palliative care earlier and more often and were more likely to stay in the intensive care unit for the month before death[16].

In the case of breast cancer, the figures are slightly different. It is suggested that this cancer is more common among people with mental disorders [17], with the incidence of patients suffering from schizophrenia being higher compared to those suffering from other mental disorders[18]. A meta-analysis by Xiping et al. showed a statistically significantly increased risk of breast cancer among people suffering from schizophrenia compared to the general population (hazard ratio = 1.18, 95% confidence interval, 1.05, 1.32)[19]. Obesity may be considered one of the possible factors among patients with schizophrenia[20]caused by a predisposition to develop metabolic syndrome, the use of antipsychotic drugs or a less active lifestyle. Obesity, in turn, can result in hyperestrogenism, leading to abnormal cell proliferation, and consequently contributing to the development of breast cancer [20]. There is also a somewhat controversial view that there is a link between hyperprolactinaemia, which is caused not only by some antipsychotics, but also by disorders of the hypothalamic-pituitarygonadal axis among people suffering from schizophrenia and breast cancer [21]. Several studies have shown that women with higher levels of prolactin are more likely to develop this cancer, but the results are inconclusive. This is confirmed by a long-standing Finnish study that showed an increased risk of breast cancer after at least 5 years of exposure to antipsychotic drugs that increase prolactin levels (corrected OR 1.56 [1.27-1.92], while a shorter exposure, similar to as second-generation drugs that did not cause hyperprolactinaemia were not associated with an increase in incidence [22]. However, this study was critically assessed from the point of view of the interpretation of the odds ratio and its limitations. The study design and results found that it was not possible to assess whether prolactin-sparing antipsychotics are associated with a lower risk of breast cancer than prolactin-increasing antipsychotics [23].On the other hand, *De Hert et al.* did not show a correlation between the chronic use of antipsychotic drugs and an increased risk of developing breast cancer, therefore it can be concluded that other risk factors are of greater importance [24]. One study found a genetic link between schizophrenia and breast cancer, with an estimated percentage of genetic overlap of 0.14 [25]. Concerning the cited information, the conclusions of the meta-analysis carried out by *Hwong et al.*, which show that women suffering from schizophrenia are half as likely to undergo mammographic screening tests, are disturbing [26].

The first generation of antipsychotic drugs	Second generation of antipsychotic drugs
 Phenothiazine derivatives (volrifluoperazine, perphenazine, prochlorperazine, acetophenazine, trifluorpromazine, mesoridazine, levomepromazine, chlorpromazine, promazine, perazine, fluphenazine) Butyrophenone derivatives (haloperidol, droperidol) Thioxanthene derivatives (thiotixene, chlorprothixene, flupentixol, zuclopenthixol, clopenthixol) Dibenzoxazepine derivatives (loxapine) 	 Risperidone Olanzapine Quetiapine Ziprasidone Aripiprazole Paliperidone Asenapine Lurasidone Iloperidone Cariprazine Brexpiprazole Clozapine

 Table 1. Antipsychotics by generation[27, 28]

A decrease in the incidence of colorectal cancer has been demonstrated among patients with schizophrenia (RR = 0.82, 95% CI 0.69–0.98), and this has been demonstrated especially in men (RR = 0.89, 95% CI 0.81 -0.98)[8]. However, on the other hand, a Canadian study of people with severe mental illness (for example, schizophrenia, bipolar disorder or major depressive disorder) and diagnosed colorectal cancer had a lower survival and less therapy, both surgery and radiation or chemotherapy [29].

Similar data were obtained when assessing the risk of developing prostate cancer. Based on the analysis of 5 studies, all of them had a lower incidence rate of this cancer, ranging from 0.49 to 0.76 [30]. The decrease in testosterone levels as a result of taking antipsychotic drugs may contribute to this [30] and this has been shown especially in people taking chlorpromazine[31]. It should be emphasized, however, that the second-generation antipsychotics, often used, do not cause hyperprolactinaemia, and therefore they may not have an effect reducing the risk of prostate cancer, if the increased level of prolactin is considered to be the protective effect of prostate cancer [30].

It should be noted that despite the predisposition of people with schizophrenia to addiction to stimulants, low physical activity, the increase in the risk of cancer in some studies was not very high. Therefore, there are speculations about schizophrenia as a protective factor, which may be due to genetic factors [32].

As previously mentioned, people with schizophrenia die much earlier than healthy people. The situation is no different in the case of their cancer. It has been proven that patients with schizophrenia have a 50% higher risk of dying from cancer compared to the general population[18]. Regarding individual neoplasms, the greatest increase in risk due to neoplasms was obtained in breast cancer (RR = 1.97, 95% CI 1.38-2.83), followed by lung cancer (RR = 1.93, 95% CI 1.46–2.54) and colon cancer (RR = 1.69, 95% CI 1.60–1.80), in the case of prostate cancer, the increase was not statistically significant. A slightly higher risk of death in breast and lung cancers was found in women[33].

The effect of antipsychotic drugs used in the treatment of schizophrenia on neoplasm, which has already been briefly mentioned, is noteworthy. Experiments in rodents have shown the possibility of an increased risk of cancer of the pituitary, breast, liver, thyroid gland and pancreas. It should be emphasized, however, that due to the different metabolism of humans and rodents, the doses used may not cause an increased risk of disease [34]. Moreover, the phenothiazine derivatives show a cytotoxic effect in vitro [35], thanks to which they could possibly be used in oncological therapies. Clozapine, in turn, has a toxic effect on the bone marrow which may result in agranulocytosis and potentially increase the risk of leukemia [34]. Even if the use of these drugs could result in an increased risk of developing a malignant neoplasm, it is assumed that the ratio of benefits of the treatment of patients with schizophrenia to the risk of [34]. The latest reports and ongoing research allow us to hope for the use of antipsychotic drugs as new treatment options for certain types of cancer (Table 2).

Table 2. Reports and ongoing studies on the use of antipsychotic drugs in cancer therapy[36–39]

Antipsychotic drug	Tumor	The mechanism of action
Thioridazine	Squamous cell	G0 / G1 cell cycle arrest in combination
	carcinoma of the	with radiation therapy; induction of
	esophagus	apoptosis and reduction of Bcl-2 and
		BclxL expression; inhibition of the PI3K-
		AK-mTOR oncogenic pathway
Pimozide	Cancer of the liver, bile	Inhibition of cell proliferation by arrest of
	ducts and pancreas	the cell cycle in the G0 / G1 phase
Trifluoperazine	Colon cancer	Inhibition of proliferation; induction of
		apoptosis; cell arrest in G0 / G1 phase;
		synergistic effect with 5-fluorouracil and
		oxaliplatin in colorectal cancer cells
Pimozide	Colon cancer	Inhibition of the Wnt / β -catenin
		signaling pathway
Chlorpromazine	Glioblastoma	Interference with Wnt / β -catenin
(ongoing clinical trial		signaling; epigenetic modification of
NC104224441)		histone deacetylase and induction of
TT 1 ' 1 1		autophagy
Haloperidol	Glioblastoma	Inhibiting the growth of glioblastoma
		cells; cell cycle arrest in G2 / M phase;
D' '1		induction of apoptosis
Pimozide	Melanoma,	Anti-dominographic effects
	neuroblastoma	~
Pimozide	Leukemia, prostate	Sensitizing cells to radiation; inhibition
	cancer	of STAT-3 and STAT-5 signaling
		proteins

Summary

The information we provide allows us to see the relationship between the occurrence of schizophrenia and the predisposition to developing malignant neoplasms. In breast, prostate and colon cancer, schizophrenia can probably be considered a protective factor. Despite the unhealthy lifestyle often pursued by patients with schizophrenia, cancers with an increased risk of developing the disease appear to be disproportionately increased. Despite reports of possible negative effects of some antipsychotic drugs on cancer, hope is currently placed in their use in anti-cancer therapy.

References

1. Schizophrenia. https://www.who.int/news-room/fact-sheets/detail/schizophrenia. Accessed 16 May 2022

- 2. Stilo SA, Murray RM (2019) Non-Genetic Factors in Schizophrenia. Curr Psychiatry Rep. https://doi.org/10.1007/S11920-019-1091-3
- 3. ICD-10 Version:2019. https://icd.who.int/browse10/2019/en#/F20-F29. Accessed 16 May 2022
- 4. Balhara YPS, Verma R (2012) Schizophrenia and suicide. East Asian Arch Psychiatry 22:126–133
- 5. Oud MJ, Meyboom-De Jong B (2009) Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care. BMC Fam Pract. https://doi.org/10.1186/1471-2296-10-32
- Dieset I, Andreassen OA, Haukvik UK (2016) Somatic Comorbidity in Schizophrenia: Some Possible Biological Mechanisms Across the Life Span. Schizophr Bull 42:1316– 1319
- 7. Kritharides L, Chow V, Lambert TJR (2017) Cardiovascular disease in patients with schizophrenia. Med J Aust 206:91–95
- 8. Li H, Li J, Yu X, Zheng H, Sun X, Lu Y, Zhang Y, Li C, Bi X (2018) The incidence rate of cancer in patients with schizophrenia: A meta-analysis of cohort studies. Schizophr Res 195:519–528
- 9. Borovcanin MM, Vesic K (2021) Breast cancer in schizophrenia could be interleukin-33-mediated. World J psychiatry 11:1065–1074
- 10. Momen NC, Plana-Ripoll O, Agerbo E, et al (2020) Association between Mental Disorders and Subsequent Medical Conditions. N Engl J Med 382:1721–1731
- 11. Pettersson D, Gissler M, Hällgren J, Ösby U, Westman J, Bobo W V. (2020) The overall and sex- and age-group specific incidence rates of cancer in people with schizophrenia: a population-based cohort study. Epidemiol Psychiatr Sci. https://doi.org/10.1017/S204579602000044X
- 12. Korpela H, Miettunen J, Rautio N, Isohanni M, Järvelin M-R, Jääskeläinen E, Auvinen J, Keinänen-Kiukaanniemi S, Nordström T, Seppälä J (2020) Early environmental factors and somatic comorbidity in schizophrenia and nonschizophrenic psychoses: A 50-year follow-up of the Northern Finland Birth Cohort 1966. Eur Psychiatry. https://doi.org/10.1192/J.EURPSY.2020.25
- 13. Zhuo C, Zhuang H, Gao X, Triplett PT (2019) Lung cancer incidence in patients with schizophrenia: meta-analysis. Br J Psychiatry 215:704–711
- 14. Sagud M, Vuksan-Cusa B, Jakšic N, Mihaljevic-Peleš A, Kuzman MR, Pivac N (2018) Smoking in Schizophrenia: an Updated Review. Psychiatr Danub 30:S216–S223
- 15. Bushe CJ, Hodgson R (2010) Schizophrenia and cancer: in 2010 do we understand the connection? Can J Psychiatry 55:761–767
- Viprey M, Pauly V, Salas S, Baumstarck K, Orleans V, Llorca PM, Lancon C, Auquier P, Boyer L, Fond G (2021) Palliative and high-intensity end-of-life care in schizophrenia patients with lung cancer: results from a French national population-based study. Eur Arch Psychiatry Clin Neurosci 271:1571–1578

- Girardi P, Schievano E, Fedeli U, Braggion M, Nuti M, Amaddeo F (2021) Causes of mortality in a large population-based cohort of psychiatric patients in Southern Europe. J Psychiatr Res 136:167–172
- 18. Nordentoft M, Plana-Ripoll O, Laursen TM (2021) Cancer and schizophrenia. Curr Opin Psychiatry 34:260–265
- Xiping Z, Shuai Z, Feijiang Y, Bo C, Shifeng Y, Qihui C (2019) Meta-analysis of the Correlation Between Schizophrenia and Breast Cancer. Clin Breast Cancer 19:e172– e185
- 20. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371:569–578
- Büschlen J, Berger GE, Borgwardt SJ, Aston J, Gschwandtner U, Pflueger MO, Kuster P, Radü EW, Stieglitz RD, Riecher-Rössler A (2011) Pituitary volume increase during emerging psychosis. Schizophr Res 125:41–48
- 22. Taipale H, Solmi M, Lähteenvuo M, Tanskanen A, Correll CU, Tiihonen J (2021) Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland. The lancet Psychiatry 8:883–891
- 23. Andrade C (2021) Understanding the Limitations of the Odds Ratio in a Case-Control Study of the Association Between Breast Cancer and Exposure to Antipsychotic Drugs. J Clin Psychiatry. https://doi.org/10.4088/JCP.21F14319
- 24. De Hert M, Peuskens J, Sabbe T, Mitchell AJ, Stubbs B, Neven P, Wildiers H, Detraux J (2016) Relationship between prolactin, breast cancer risk, and antipsychotics in patients with schizophrenia: a critical review. Acta Psychiatr Scand 133:5–22
- 25. Lu D, Song J, Lu Y, et al (2020) A shared genetic contribution to breast cancer and schizophrenia. Nat Commun. https://doi.org/10.1038/S41467-020-18492-8
- Hwong A, Wang K, Bent S, Mangurian C (2020) Breast Cancer Screening in Women With Schizophrenia: A Systematic Review and Meta-Analysis. Psychiatr Serv 71:263– 268
- 27. Chokhawala K, Stevens L (2022) Antipsychotic Medications. StatPearls
- 28. First-Generation Antipsychotics: An Introduction Psychopharmacology Institute. https://psychopharmacologyinstitute.com/publication/first-generation-antipsychoticsan-introduction-2110. Accessed 20 May 2022
- 29. Mahar AL, Kurdyak P, Hanna TP, Coburn NG, Groome PA (2020) The effect of a severe psychiatric illness on colorectal cancer treatment and survival: A populationbased retrospective cohort study. PLoS One. https://doi.org/10.1371/JOURNAL.PONE.0235409
- 30. Torrey EF (2006) Prostate cancer and schizophrenia. Urology 68:1280–1283
- 31. Mortensen PB (1992) Neuroleptic medication and reduced risk of prostate cancer in schizophrenic patients. Acta Psychiatr Scand 85:390–393

- 32. Hodgson R, Wildgust HJ, Bushe CJ (2010) Cancer and schizophrenia: is there a paradox? J Psychopharmacol 24:51–60
- 33. Ni L, Wu J, Long Y, Tao J, Xu J, Yuan X, Yu N, Wu R, Zhang Y (2019) Mortality of site-specific cancer in patients with schizophrenia: a systematic review and meta-analysis. BMC Psychiatry. https://doi.org/10.1186/S12888-019-2332-Z
- 34. Fond G, Macgregor A, Attal J, Larue A, Brittner M, Ducasse D, Capdevielle D (2012) Antipsychotic drugs: pro-cancer or anti-cancer? A systematic review. Med Hypotheses 79:38–42
- 35. Nordenberg J, Fenig E, Landau M, Weizman R, Weizman A (1999) Effects of psychotropic drugs on cell proliferation and differentiation. Biochem Pharmacol 58:1229–1236
- 36. Lianos GD, Alexiou GA, Rausei S, Galani V, Mitsis M, Kyritsis AP (2022) Repurposing antipsychotic drugs for cancer treatment: current evidence and future perspectives. Expert Rev Anticancer Ther 22:131–134
- 37. Avendaño-Félix M, Aguilar-Medina M, Bermudez M, Lizárraga-Verdugo E, López-Camarillo C, Ramos-Payán R (2020) Refocusing the Use of Psychiatric Drugs for Treatment of Gastrointestinal Cancers. Front Oncol 10:1452
- 38. Zhuo C, Xun Z, Hou W, et al (2019) Surprising anticancer activities of psychiatric medications: Old drugs offer new hope for patients with brain cancer. Front Pharmacol 10:1262
- Elmaci I, Altinoz MA (2018) Targeting the cellular schizophrenia. Likely employment of the antipsychotic agent pimozide in treatment of refractory cancers and glioblastoma. Crit Rev Oncol Hematol 128:96–109