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Applications of Pharmacoepidemiology in Cancer Research

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ABSTRACT

Differences in cancer types and anticancer drug responses, involved the cancer research programs in a challenging area, required integration of several fields. Combination of clinical pharmacology and epidemiology termed as pharmacoepidemiology in cancer research projects ,providing cancer therapy researchers with investigation of different drug responses among individuals in terms of treatment, efficacy , survival rate and adverse effects in a distinct large population . According to the published pharmacoepidemiological evidences, various statically observational results obtained about effects of non-anticancer drugs(e.g. antidepressant adherence and antihypertensive medications) in breast cancer , individual effect of anticancer drugs (e.g. Statin or Metformin) in epithelial ovarian cancer, comparison of individual and association effects of two anticancer drugs (e.g. individual or joint use of Statin and Metformin) on overall pancreatic cancer survival, comparison of two anticancer drugs(e.g. azacitidine and decitabine) in myelodysplastic syndromes and role of racial variation (e.g. skin color of women ; black and white) in advanced epithelial ovarian cancer therapy. In this paper, i will discuss how the researches obtained their findings based on pharmacoepidemiology methods. This paper is useful for potential researchers to utilize these findings and their procedures for investigation of anticancer drug effects in a well-defined population in order to assess the potential health hazard accompanied with drug use in real life and to quantify the appropriate public health effect of marketed anticancer drugs.

Keywords: pharmacoepidemiology, Cancer therapy, drug effects, cancer survival, health hazard.

I. INTRODUCTION

Cancer is the second cause of morbidity among high risk diseases in the human population [1] .Although several anticancer drugs marketed and recently under investigation in clinical trials but their survival rate, efficacy, treatment power and adverse effects in a distinct population after post marketing, require further evaluations and quantifications. Integration of pharmacoepidemiology to cancer research studies for achieving these assessments, showed its significant role in reduction of health hazard and improvement in public health. Pharmacoepidemiology, itself deals with studying impacts of medical drugs at the population level . Characterization of patterns use of drug and assessment of potential health hazard accompanied with drug use in real life , confirming the beneficial drug impact , quantification of the appropriate public health and effects of marketed drugs ,are important aims of the pharmacoepidemiology . According to available and published references, investigators utilized applications of pharmacoepidemiology in assessment of anticancer drug in different types of cancers such as breast cancer, epithelial ovarian cancer, Pancreatic Adenocarcinoma, Myelodysplastic syndromes and so on.[2-4] They used mostly " the Surveillance, Epidemiology and End Results (SEER)-Medicare" database for their sample studies .The SEER-Medicare data interprets correlation of two large population-based sources of data that give comprehensive information about Cancer Medicare beneficiaries. The data provided from the Surveillance, Epidemiology and End Results (SEER) External Web Site (https://seer.cancer.gov) which is a policy program of cancer registries that gather clinical, analytical and death causes information and the Medicare claims related to covered health care services for cancerous patients, for a time period of their Medicare registration until their death. The survival analysis methods used for analyzing the expected period of time until death event. The researchers used mostly common types of survival analysis methods such as Kaplan Meier , Time-varying Cox proportional hazard models for estimation of Hazard ratios (HRs) and their associated confidence

intervals(CLs) and Propensity score for matching step of creation of two similar cohorts (confounder control) .[4-5] They obtained different results and observations for different cancer studies, some of the results showed strong association between drugs and survival rate while in some cases there were no significant association between them. In this paper , I aim to demonstrate significant role and applications of pharmacoepidemiology in cancer studies with focus on recent published papers.

II. METHODS AND MATERIAL

A. Estimation of the impact of the receiving breast cancer diagnosis on antidepressant adherence among depressed women:

The aim of this research is whether long –course of antidepressant treatment can reduce depression symptoms or cancer diagnosis among depressed women, may have functional role in disruption of progressing depression therapy. The researchers used SEER-Medicare administrative claims, they identified women aged 65+ with early recognized breast cancer between 2008 and 2011, who had depression and treated with antidepressants just one year before pre-recognizing the cancer. They compared antidepressant adherence (compliance) among depressed women with breast cancer and the same women without breast cancer using GEE(generalized estimation equations).The estimation of antidepressant done using ratio of days , one year before and after the index date . The results of the studies demonstrated that Mean antidepressant coherence was resembling for both groups of 1142 pre –existing depressed women with breast cancer and 1142 pre-existing depressed women without breast cancer in the corresponding date (all around 0.71) .There was an approximately 0.01 adherence decline in cancerous group with almost similar decline in non-cancerous group (0.19). Nevertheless, considerable proportion of patients had inadequate compliance to antidepressants in the post-diagnosis period ,and around 40% of patients in both groups stopped antidepressant treatment over the prescribed period. Finally , The researchers concluded that there was not any significant association with receiving a breast cancer diagnosis and antidepressant adherence in cancer group and almost the same result found for a non-cancer group among depressed women receiving antidepressant .However, adherence was weak in both group . Ensuring appropriate and sufficient progressing depression treatment is significant for improving cancer treatment and life quality of patient in the long course. [6].

B. Individual and associated properties of Metformin and Statin on overall pancreatic cancer survival

Recent studies and evidences suggests that there is a significant association between single use of statin and metformin with declined cancer fatality . However, their differential and linked impacts on pancreatic cancer survival are unclear . The scientists already identified a cohort of 12,572 patients aged 65+ suffering from primary pancreatic ductal adenocarcinoma (PDAC) recognized between 2008 and 2011 from the SEER – Medicare –inked database . Confirmation of exposure to Metformin and Statins was done by Medicare Prescription Drug Event files. Survival models such as Cox proportional hazards models and Time-varying predictors and coefficients fixed for PSM were used for assessment of the coordination while controlling potential impairs(confounders) .The Result of the study demonstrated that 7.56% of patients took metformin solely, 35.84% used statin alone , and 19.45% were joint users. According to the statistical results, statin treatment showed significant association with improved overall survival while metformin treatment did not show significant association with overall survival . No considerable impact was ascertained for joint users of metformin and statin. Although their finding requires more investigation but their results contribute in the evidence list of qualified anticancer properties .[7]

C. Effects of common antihypertensive medications on risk of adverse impacts of Breast cancer

To understand if the common antihypertensive drugs effect the risk of adverse impacts of breast cancer, researchers identified 14,766 women between ages 66 and 89 years recognized with incident stage I/II breast cancer between 2007-2011 from the SEER Medicare database. They utilized Time-varying Cox proportional hazard models for estimation of Hazard ratios (HRs) and their associated confidence intervals(CLs). The results illustrated that there were 791 women with SBCEs, 627 women with breast cancer recurrences, and 237 breast

cancer deaths identified over study period of 3 years . Treatment with diuretics and β-blockers may be coped with 29% higher risks of a SBCE, 36% recurrence and 51% breast cancer death. While comparing to non-users, β-blockers users showed 41% higher risk of breast cancer death. In addition , use of calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers did not show any association with risks of breast cancer impacts. While the researchers confirmed safety of most antihypertensive medications corresponding to breast cancer outcomes , but still more investigation required for diuretics and β-blockers with respect to breast cancer outcomes.[8]

D. Association of statin use with survival in women group suffering from epithelial ovarian cancer

Recently on the basis of observational studies ,researchers suggested the effectiveness of statin therapy in survival percentage in epithelial ovarian cancer patients .As a sample of study , they used a nationally representative elderly population suffering from epithelial ovarian cancer . For extraction of data on statin prescription fills, population features, initial treatment, comorbidity and survival , they used the linked Surveillance, Epidemiology, and End Results (SEER) and Medicare claims data for the sample group in 2007-2009. They utilized Cox regression models for examination of the relationship between statin use and overall survival. A prescription filled for statin for 42.6% of patients who already exposed to surgical resection among 1431 total sample group. The large percentage of statin users (89%) were treated with a lipophilic formulation. The results of the studies illustrated that Mean overall survival among statin takers was 32.3months while it was 28.8 months for non-takers($p<0.0001$). As a consequence a 34%decline in morbidity was accompanied with statin treatment regardless of age, race , economic situation ,platinum therapy and disorder co-occurring .As a conclusion , this study is very helpful in evaluation of the effect of statin therapy in ovarian cancer survival in elderly patients who already underwent surgical resection. [9].

E. Metformin effect on overall survival in ovarian cancer by a SEER-Medicare analysis:

In this observational studies a sample group with first epithelial ovarian cancer between 2007 and 2011 in SEER –Medicare database were identified , for finding the Medicare claims files , Comorbidities, process , and cancer therapy, ICD-9 and HCPCS codes used. Cox Proportional Hazards survival model utilized for overall survival evaluation among metformin users and non-users .For confounder control , matching of metformin users and non-users done by propensity scores. And finally discrete time survival analysis with pooled logistic regression (PLR) applied for evaluation of dosage effect on survival . As a result, there were no any mathematically considerable relationship between metformin taking and overall survival in a matched group of 360 ovarian cancer patients . However, the effectiveness of metformin use can be detected in a specific subgroups of patients .[10].

F. Comparison of clinical efficacy of azacitidine and decitabine in aged old patients suffering from myelodysplastic syndromes.

Approval of both azacitidine and decitabine confirmed for myelodysplastic syndromes therapy in the USA while the approval for decitabine is not established in Europe due to failure in its survival effect in randomized investigations. Researches already compared these two drugs on the basis of observational studies, they identified Patients with myelodysplastic syndromes.(MDS) , from SEER)-Medicare linked database in the USA who treated with≥ 10 doses of both drugs . They utilized Kaplan-Meier methods and multivariate Cox proportional hazards models for survival estimation from hypomethylating agents(HMA) and adjustment of covariates respectively. They also conducted a specific analysis for subgroup of patients with refractory anaemia with excess blasts (RAEB). Their observations illustrated that median survival was 15 months with no characteristic survival effect emerged from decitabine versus azacitidine assessment test , As a result of the studies , they found that There were no considerable survival difference between azacitidine and decitabine in patients suffering from MDS including refractory anaemia with excess blasts . In addition to their finding, there was significant difference in survival months for azacitidine-treated RAEB patients and AZA-001 clinical trial , 11 months and 24.5 months respectively .[11]

G. Role of racial variation in advanced epithelial ovarian cancer therapy:

The purpose if this research was to investigate whether there is any association between guideline-recommended care treatment with mortality rate between black and white skinned women suffering from advanced epithelial ovarian cancer. The researchers supervised an observational study using linked SEER Medicare claim between 1995-2007. In this research study, by utilization of Kaplan-Meier analysis , Cox regression and matching step for creation of two similar cohort by propensity score , long term survival assessment performed for 4,695 women including black and white individuals bearing epithelial ovarian cancer in stage III and IV .They found the relationship between race , stage and survival rate among patients who were treated with guideline-recommended care and those who incompletely treated .The results of their study showed that probability of black women to die was more than that white women(unadjusted hazard ratio). The possibility of receiving guideline-recommended care for black women is lesser than white women(54% versus 68%; P<.001). According to Cox proportional hazards models, there were no mortality differences among black women with incomplete treatment (adjusted HR 1.04; 95% CI 0.85-1.26)than white women with complete treatment(adjusted HR 1.04; 95% CI 0.85-1.26). Confirmation of these findings done by survival analysis matched by propensity score .To sum up this report study , there is an association between receiving recommended treatment and lower survival rates among women with advanced epithelial ovarian cancer. [12].

III. RESULTS AND DISCUSSION

From one side ,variation in cancer types and anticancer responses among individuals, and from other side , high demand for urgent cancer treatment due to increasing death rate because of cancer , required integration of different science fields to support a strong multiple treatment in order to provide an appropriate cancer therapy .Hence pharmacology and epidemiology fields combined to investigate drug effects in specific diseases such as cancers. The combination of pharmacology and epidemiology is known as pharmacoepidemiology .The anticancer drugs , when marketed , do not investigate in clinical trials any more . So, their efficacy ,adverse effect and survival rates should be analyzed to achieve maximum beneficiary. Pharmacoepidemiology by utilizing survival analysis methods such as Kaplan Meier ,Cox Proportional Hazard models and the Surveillance, Epidemiology and End Results (SEER)-Medicare" database and so on, aids in finding observational results and effects of anticancer drugs in a large population and to estimate survival rate among patients with specific cancer type , drugs association degree ,comparison of individuals and joint anticancer and non-anticancer drugs and to identify role of other factors in cancer treatment such as race ,skin color and other relevant factors . These estimations and evaluations are essential for appropriate cancer therapy , achieving higher drug effectiveness ,minimizing adverse effects , reduction in morbidity rate and increasing survival rate in cancerous patients.

IV. CONCLUSION

Pharmacoepidemiology as an integrated fields of pharmacology and epidemiology , plays significant role in cancer therapy .By using different survival analysis methods of the field in cancer therapy, different drug response among individuals in terms of treatment, efficacy, survival rate and adverse effects in a large population can be achieved which are very valuable for proper cancer treatment, increasing survival rate , minimizing adverse effects and morbidity rate.

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