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Prevalence and Risk Factors Associated with Upper Gastrointestinal Malignancies in Post-Menopausal Patients on Hormone Replacement Therapy: A Population-Based Study

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ABSTRACT

Background and Aim: In the United States, approximately 40% of post-menopausal women use hormone replacement therapy (HRT); estrogen with or without progesterone. Treatment of menopausal symptoms such as hot flashes, urogenital atrophy is an indicator of short-term use of HRT. However, in some cross-sectional studies, it is reported that women use HRTs for far longer than the intended duration. Over the years, results for most studies showing benefits of HRT were only significant for short-term use of the drug. Grodstein et al. reported decreased incidence of coronary artery disease in current users, but not among ever, past or all use groups. We believe hazardous effects of HRTs are seen in among ever, past groups. The risk of breast cancer, endometrial cancer and cholecystitis is established to be associated with increasing duration of use and risk remained elevated even 5 years after discontinuation. Though we have studies highlighting effects of HRT and reproductive malignancies, the impacts of long-term use of HRT and development of gastrointestinal (GI) malignant neoplasms is lacking. Therefore, we decided to carry out a study highlighting the prevalence of upper GI tumors (gastric, esophageal and pancreatic cancers) in postmenopausal women who have used HRT.

Methodology: A validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States from 1999 to September 2022 was utilized to construct this study. Females aged 65 years and above were included in the study. Patients with autoimmune diseases were excluded. Three separate multivariate regression analyses, assessing the risk of developing esophageal, stomach, and pancreatic cancer, were performed by controlling for potential cofounders. A two-sided P value <0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Results: 79,368,988 individuals were screened in the database and 11,177,050 were selected in the final analysis after accounting for inclusion and exclusion criteria. The baseline characteristics of patients with esophageal, gastric, and pancreatic cancer is seen in Table 1. Three separate multivariate regression analyses were performed to assess the risk of developing esophageal, gastric, and pancreatic cancer. The odds of having Gastric cancer (GC) in HRT users was increased at 1.74 (95% CI 1.51-1.99), Similarly, the odds of have Pancreatic cancer (PC) in HRT user was also increased at 1.40 (95% CI 1.26-1.56 (Table 2).

Conclusion: Our study shows that, even after adjusting for typical risk variables, gastric and pancreatic cancer are frequently observed among HRT users. This adds to the literature to spread awareness to clinics that the effects HRT are not only limited to female reproductive system as it's use tend to involve parts of the gastrointestinal system.

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Introduction

Menopause is defined as amenorrhea for 12 months caused by insufficient production of ovarian hormones [1,2]. It is commonly accompanied by bothersome symptoms like hot flashes, genitourinary symptoms, and mood changes resulting from low levels of estrogen [3-5]. Since its introduction to the market, Hormone Replacement Therapy (HRT) has been proven to be the most effective therapy for the majority of these symptoms [1,2].

In fact, in 1995 more than 38% of US women were using short-term HRT to treat menopause symptoms [5]. HRT was also used to prevent chronic diseases like osteoporosis and cardiovascular diseases [6]. Nonetheless, HRT use has significantly decreased after several reports of major side effects There is still much debate about the risks and benefits of HRT. While the Women Health Initiate (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) found an increased risk of CVD with HRT use, other studies showed contradictory results [2,5,6]. Similarly, the relationship between HRT and neurodegenerative diseases like Alzheimer's disease and Parkinson's disease on one hand, and breast cancer on the other hand were inconclusive [2]. Nelson et al demonstrated a positive impact on the cardiovascular disease's outcomes and mortality in patients currently using HRT compared to ever and past users. Moreover, HRT contributed to a significant increase in the risk of thromboembolism, depending on the dose and type of HRT used. Various meta-analyses pointed to an increased risk of breast cancer in patients currently using HRT. It was also evident in the literature that estrogen-only HRT was associated with higher risk of endometrial cancer, while estrogen-progestin combination HRT turned out to be protective against it. Notably, the WHI aligned with a meta-analysis assessing the risk of colon cancer in HRT users, and confirmed its findings of increased risk of colon cancer in HRT users [6].

Although the relationship between HRT and various malignancies has already been established, little evidence supports any relation between HRT use and GI malignancies. Therefore, we decided to carry out a study highlighting the prevalence of upper GI tumors (gastric, esophagus, and pancreatic cancers) in postmenopausal women who have used HRT.

Materials and Methods

Explorys, a validated, multicenter, and regularly updated database developed by IBM Corporation, Watson Health [IBM corporation], was used to gather data from our cohort. Explorys is made up of the electronic health data of 26 different healthcare systems, with a total of about 360 hospitals and more than 70 million patients nationally. Disorders are described in Explorys using SNOMED-CT, or Systematized Nomenclature of Medicine-Clinical Terminology. The diagnosis is made by the individual healthcare professionals, who then enter the information into the database as SNOMED-CT codes.

The database gathers huge volumes of deidentified data from both inpatient and outpatient settings that can be organized into various cohorts, according to the clinical component under investigation. Explorys does not keep records of specific patient information, such as test or imaging findings. Because the data are acquired from several organizations, different organizations, and subsequently healthcare providers, may utilize different techniques to identify certain medical disorders. Because of the way the database is set up, it is very dependent on individual organizations providing accurate data, which makes it impossible to examine the type of diagnosis. The Institutional Review Board is not required because Explorys is a platform that complies with the Health Insurance Portability and Accountability Act (HIPAA). The use of this database has been approved in a number of specialties, including gastroenterology, hematology, and cardiology [7-11].

Patient Selection

A cohort of patients with a SNOMED-CT diagnosis of "Hormone replacement therapy", "Esophageal cancer" "Gastric cancer" "Pancreatic cancer" between 1999 and September 2022 was identified. Females aged 65 years and above were included in the study. We excluded individuals who have had a diagnosis of any "Autoimmune diseases".

Covariates

Confounding factors associated with the development of esophageal, gastric and pancreatic cancer were identified and collected if SNOMED-CT diagnoses were available. These were alcoholism, smoking, obesity, gastroesophageal reflux (GERD), Helicobacter pylori (H-pylori) infection, Type II diabetes mellitus (T2DM).

Statistical Analysis

To account for confounding from the covariates listed above, we conducted 1024 searches to explore every probability. A univariate analysis was conducted initially for all the variables. A multivariate analysis using backward stepwise logistic regression was performed to calculate the risk of developing esophageal, gastric and pancreatic cancer. A conservative significance threshold of 0.01 was used to determine the qualification of data entry into or deletion form the model. Alcoholism, smoking, obesity, GERD, H-pylori infection, T2DM were included in the logistic regression. A two-sided P value <0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Result

Among the 11,177,050 individuals screened in this database, there were a total of 8040 subjects with Esophageal cancer, 12,400 with Gastric cancer, 25,980 with Pancreatic cancer. Interestingly, majority of patients with Esophageal, Gastric, Pancreatic cancer had T2DM (Table 1). In multivariate analysis, the odds of having Gastric cancer (GC) in HRT users was increased at 1.74 (95% CI 1.51-1.99), Alcoholism 2.33 (95% CI 2.05-2.64), Smokers 2.62 (95% CI 2.47-2.78), H-pylori infection 7.63 (95% CI 2.47-2.78). The odds of have Pancreatic cancer (PC) in HRT user was also increased at 1.40 (95% CI 1.26-1.56), Alcoholism 1.76 (95% CI 1.59-1.94), Smokers 2.00 (95% CI 1.92-2.09), Obesity 1.03 (95% CI 0.99-1.06), patient with T2DM 3.36 (95% CI 3.27-3.49). The odds of having Esophageal cancer (EOC) in HRT users was 0.93 (95% CI 0.79-1.08), Alcoholism 2.35 (95% CI 2.09-2.63), Smoker 1.50 (95% CI 1.40-1.60), Obesity 0.54 (95% CI 0.50-0.57), GERD 9.88 (95% CI 9.40-10.38), H-pylori infection 2.63 (95% CI 2.18-3.15) (Table 2)

Table 1: Baseline characteristics of patients with esophageal, gastric, and pancreatic and control (patients without cancer)

	Esophageal cancer (%)	Gastric cancer (%)	Pancreatic cancer (%)	Control (%)
Alcohol	260 (3.23)	190 (1.53)	360 (1.38)	66,680 (0.59)
Smoker	950 (11.81)	1,170 (9.44)	2,190 (8.42)	413,770 (3.71)
Obesity	1,190 (14.80)	2,150 (9.43)	3,840 (14.78)	1,000,460 (8.98)
Gastroesophageal reflux	3,820 (47.51)	5,450 (43.95)	9,350 (35.98)	1,744,670 (15.67)
Helicobacter pylori infection	40 (0.49)	110 (0.88)	110 (0.42)	15,890 (0.14)
Diabetes mellitus type 2	2,080 (25.87)	3,950 (31.85)	9,850 (37.91)	1,584,360 (14.23)
HRT use	100 (1.24)	130 (1.04)	270 (1.03)	84,500 (0.75)
Total	8,040	12,400	25,980	11,130,630

Abbreviations: HRT, hormone replacement therapy

Table 2: Multivariate regression analysis assessing the risk of developing esophageal, stomach, and pancreatic cancer compared to control

	Esophageal Cancer OR (95% CI)	P-value	Gastric Cancer OR (95% CI)	P-value	Pancreatic Cancer OR (95% CI)	P-value
Alcoholism	2.35 (2.09-2.63)	<0.001	2.33 (2.05-2.64)	<0.001	1.76 (1.59-1.94)	0.07
Smoking	1.50 (1.40-1.60)	<0.001	2.62 (2.47-2.78)	<0.001	2.00 (1.92-2.09)	<0.001
Obesity	0.54 (0.50-0.57)	<0.001	X	X	1.03 (0.99-1.06)	0.07
GERD	9.88 (9.40-10.38)	<0.001	X	X	X	X
Helicobacter pylori infection	2.63 (2.18-3.15)	<0.001	7.63 (6.56-8.81)	<0.001	X	X
HRT use	0.93 (0.79-1.08)	0.36	1.74 (1.51-1.99)	<0.001	1.40 (1.26-1.56)	<0.001
T2DM	X	X	X	X	3.36 (3.27-3.49)	<0.001

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; HRT, hormone replacement therapy; OR, odd ratio, PPI, proton-pump inhibitor; T2DM, type 2 diabetes mellitus; X, variable not included in multivariate regression analysis.

Discussion

In our study, post-menopausal women on HRT were found to have increased prevalence and odds of having GC and PC. The odds remained significant even after controlling for common risk factors like smoking, alcohol consumption, obesity, GERD, H-Pylori Infection, and T2DM. Interestingly, we also observed decreased risk for esophageal cancer in the HRT population after controlling for confounding factors.

Several randomized controlled trials, epidemiologic and observational studies showed that HRT protects from the development of colorectal cancer [6,12]. Indeed, this finding was correlated with the ability of estrogen to bind to Estrogen receptor beta linked to lower risk of colorectal carcinogenesis and mortality [12]. Few articles in the literature assessed the relationship between HRT and gastric, esophageal, and pancreatic cancers. In fact, a Korean study found a decreased risk of incidence and mortality of gastric cancer in long-term HRT users without controlling for other risk factors like H-pylori infection [12]. Similarly, a systematic review and meta-analysis found a 37% decrease in the risk GC in estrogen-only HRT users and a 30% decrease in estrogen-progestin combinations HRT users, without taking into consideration confounders [13]. Likewise, studies on esophageal cancer and HRT were inconclusive. While some articles described no association between HRT and EOC, others have found HRT to decrease the risk of EOC, and Saleh et al. claimed that HRT use increases the risk of esophageal carcinoma in postmenopausal women on estrogen only as HRT have a higher risk of developing GERD and Barrett's esophagus [14-16]. The association between HRT use and PC is also debatable due to the limited evidence. Studies have suggested that estrogen may inhibit pancreatic cancer growth, while longer duration of oral contraceptive use has not been associated with an increased risk of pancreatic cancer [17,18].

Currently used hormone replacement therapy consists of estrogen pills for hysterectomized women and estrogen-progestin combinations for the rest [19,20]. Estrogen helps alleviate menopausal symptoms, while progestin prevents estrogen-induced proliferation of uterine epithelium The mechanism by which HRT affects GI tissues is not well understood. Some suggested that estrogen affects GI tissues by binding to the estrogen receptor Beta (ERB) responsible for slowing down cellular activity in these tissues. This theory was further strengthened by the observation that ERB negative gastric cancers have poor prognosis, in addition to the rapid progression of gastric cancer in patients on Tamoxifen, which have antiestrogenic effects [13]. Correspondingly, the relation between HRT and other malignancies is equivocal. While some studies showed that estrogen promotes malignancy by stimulating growth of cells like bladder and gastric tissues, others noted that it delays progression of EOC and melanoma [19]. To note, estrogen-progestin combination was associated with a higher risk of breast cancer compared to estrogen-only HRT, raising questions around the role of progestin in the development of cancer [20]. Perkins et al suggested that specific progestin types can bind to estrogen receptors and therefore further potentiate its effect on the breast tissue. Other studies claimed that progestin metabolites are capable of binding to estrogen receptors. More recent studies highlighted a direct effect of the progesterone receptor on the signals of the estrogen receptor [20].

Our population-based study comes in line with previously published studies, although most studies showed contradictory results. The strengths of our project lie in its large sample size, diverse population, and extensive multivariate regression analysis taking into consideration major risk factors for GI carcinogenesis. This study contains a number of limitations. First of all, because it is a retrospective population-based study, there are inherent restrictions on the inferences that can be made from the data. As patient information is deemed confidential, the accuracy of the data could not be verified, rendering it prone to potential errors. Furthermore, there was insufficient information regarding HRT type and duration.

Conclusion

In our study, post-menopausal women on HRT have increased prevalence and odds of having gastric cancer and pancreatic cancers. The odds remained significant when controlled for common risk factors. Interestingly, we also observed a decreased risk for esophageal cancer in the HRT population. We believe the impact of reproductive hormones on a cellular level span across the reproductive system to involve other systems of the human body. The US Preventive Services Task Force (USPSTF) agrees that evidence is lacking to guide recommendations for or against the use of HRT. We push that clinician be familiar with these associations. The decision to initiate drug use should be solely based on the patient's willingness and complete understanding of benefits and potential risk factors.

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