Peer Review File

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Reviewer Comments

Comment 1. Title, the term, population-based study, is inaccurate. In fact, this is a population based cohort study.

Reply: Thanks. We have change "population-based study" into "population-based cohort study" the title and the discussion (See title, Page 16 Line 21, and Page 18, Line 21. Highlighted in yellow.

Comment 2. Abstract. 0.136/100000 is yearly or period accumulated incidence rate must be specified.

Reply: 0.136/100000 is yearly, i.e. "0.136 per 100,000 people-years". The term "people-years" was also reported in "Tripathi R, Chen Z, Li L, Bordeaux JS: Incidence and survival of sebaceous carcinoma in the United States. J Am Acad Dermatol 2016, 75(6):1210-1215." and "Lu T, Yang X, Huang Y, Zhao M, Li M, Ma K, Yin J, Zhan C, Wang Q: Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer management and research 2019, 11:943-953."

We have modified the Abstract/Results (See Page 3, Line 14,17) and the Method (See Page 9, Line 12), Results (See Page10 Line13, Page 11 Line 7) and Discussion

(See Page 13, Line 5). All highlighted in yellow.

Comment 3. Introduction. No large-scale studies of UCDS is not the rationale for this study, at least, the authors should emphasize the clinical importance or public health significance of this study topic.

Reply: We deleted "Due to the low incidence of UCDS, no large-scale studies have described its incidence and prognosis. Hence, the choice of treatment is not based on evidence." and then added "The knowledge of UCDS will improve and protect community health by determining of public health prevention strategies, formulating health insurance policies, and identifying members of multidisciplinary treatment. Thus, this cohort analysis conducted with an aim to improve the understanding of UCDS, which is of significance from both clinical and public health perspectives." (See Page 5, Line 7-11, highlighted in yellow)

Comment 4. The introduction is simple. Although related data are rare, it is also necessary to review current knowledge on the epidemiology, treatment, incidence, and time trends of UCDS.

Reply: We add a paragraph in the introduction. "The publications available regarding UCDS are scarce, and thus, UCDS is not well understood. In terms of epidemiology, the most commonly site of UCDS as reported by researchers in East

Asia is the stomach, noted during endoscopic resection for early gastric cancer (3,4). Other sites such as pancreas and hepatobiliary organs have also been reported (5-8). Reports on the incidence of UCDS, however, are limited in the literature. Moreover, the time trends of the incidence have not been analyzed. For treatment of undifferentiated early gastric cancer, endoscopic and surgical resections are effective (3,9,10). However, for regional and metastatic undifferentiated gastric cancer and other sites of UCDS, treatment strategies are multidisciplinary without a specified value for each treatment (7,11,12).” (See Page 5 Line 12-21, highlighted in yellow)

Comment 5. Methods. More detailed information on the two SEER-based cohorts are needed, such as the size of the population covered, whether it is a fixed or dynamic cohort, how subjects were collected. In this manuscript, the authors described the patients with UCDS identified only.

Reply: We add a paragraph in the Method/Data sourse “Data collection in SEER began since 1973, from various locations and sources throughout the United States. Data of the incidence, patient demographics, tumor site, morphology, stage, treatment and follow-up are collected continuously. SEER enlarges the data captured in terms of detail and longitudinal information from expanding registries. The Surveillance Research Program in National Cancer Institute's Division of Cancer Control and Population Sciences provided the analytical tools and

methodological supports in collecting, analyzing, interpreting, and disseminating population-based statistics. We abstracted data from the Surveillance, Epidemiology, and End Results Program (www.seer.cancer.gov) SEER*Stat Database during 1975–2016, submitted in November 2018 and released in April 2019. The latest released SEER data cover approximately 34.6% of the US population (13).” (See Page 6 Line 19- Page7 Line7, highlighted in yellow)

Comment 6. The conclusions should be made without over statement, for example, “The incidence of UCDS has decreased in the past 40 years” should be specific to the people of an individual country.

Reply: We have modified the conclusion into “The incidence of UCDS had decreased in the United States in the past 40 years.” (See Page4Line1-2, Page19Line 4, highlighted in yellow)

Comment 7. Discussion. Changes in socio-economic status and medical services level should also be discussed as one of the most important reasons underlying the study findings.

Reply: We add a paragraph in the Discussion“Our study shows that low socioeconomic status is associated with the high incidence of UCDS. Previous lines of evidence show a heterogeneous correlation between socioeconomic status and

the digestive cancer incidence. First, many researchers reported a positive correlation between socioeconomic status and the incidence of the digestive cancers. In France, a study of 189,144 cancer cases reported that a low socioeconomic status is associated with a high incidence of stomach and liver cancer in both males and females; it is also associated with esophageal cancer and pancreatic cancer in males (25). In the US, studies reported that the incidence of cancer in the stomach, colorectum and liver was higher in a population with low level of income and education (26,27). In another cases, a Finnish study found that colon cancer incidence was higher among the highly educated population than in those with a basic education (28). An American study of 40,314 patients with CRC found a negative correlation between socioeconomic status and the incidence of CRC (29). In contrast, a Swedish study including 82,686 patients with colorectal cancer reported that disposable income and education level were not related to the incidence of colorectal cancer (30). Not only the inconsistency of incidence indicates the heterogeneity in tumorigenesis of undifferentiated cancers but also the differences in mortality and morbidity may reflect inequality in smoking, obesity, lack of exercise, diet, drinking, screening, and treatment (27). Therefore, our results have both public health significance and clinical importance. On the one hand, in terms of public health prevention strategies, our research identified high-risk populations for screening. The prevention strategy of cancers should be applied to all individuals, regardless of their socioeconomic status. However, screening for low-income patients and patients with a low-level of education may

reduce the unequal incidence of UCDS. Similarly, reasonable allocation of medical budgets should be considered alongside health insurance policies. On the other hand, in terms of tumorigenesis of UCDS, the high incidence of people with a low-income and education is a clue to identify the pathogenesis. Potentially, preventive measures on changing certain lifestyle choices may narrow the economic and educational health differences."(See Page 15 Line 1- Page 16 Line 7, highlighted in yellow)