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Factors associated with pancreatic cancer in Spain. What can we learn from epidemiological studies?

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The incidence of pancreatic cancer (PC) in Spain has progressively increased over the past 6 decades. Pancreatic ductal adenocarcinoma represents over 80 % of all pancreatic neoplasms (1).

REDECAN estimates 9,252 new cases of pancreatic cancer (4,743 in males, 4,509 in females) will be diagnosed in Spain for 2022 (3). GLOBOCAN predictions regarding this malignancy for 2040 amount to 10,700 cases/year, which represents an incidence increase by almost 45 % (4).

In 2020 PC was the third most common cause of cancer-related mortality in our country, after lung and colorectal cancer, with 7,427 deaths (2), and the fourth most common cause of mortality in Europe, both in males—after lung, colorectal, and prostate cancer—and in females, after breast, colorectal, and lung cancer (5). PC is therefore a malignancy with poor prognosis.

The study by Enrique Gili-Ortiz (7), published in this issue of *The Spanish Journal of Gastroenterology*, on pancreatic cancer-related mortality trends in Spain revealed a significant increase in death rates in our country, which may be partly attributed to population ageing and increased smoking, obesity, and diabetes rates. Other known factors, including chronic pancreatitis, seem to play a less significant role from a quantitative perspective.

These data confirm the results reported by other publications over the past decade since the absolute number of cancer cases diagnosed in Spain started increasing partly due to the country's population growth (in 1990, Spain had a population of 38,850,000 inhabitants; in 2000, of 40,264,000; in 2010, of 46,486,000, and in 2021, of 47,326,687 inhabitants).

However, also population ageing (age is a key risk factor for cancer development) and exposure to specific risk factors such as smoking, alcohol, pollution, obesity or sedentarism, among others, stand out. Because of a combination of said factors it may well occur that, in spite of unchanged exposure to risk factors over time, the absolute number of cases may rise as a result of the two factors mentioned initially (population growth and ageing).

The most significant environmental factor in PC, possibly the only one firmly established, is tobacco smoking. It likely is a contributing cause in approximately 20-25 % of all PCs. Data from meta-analyses have revealed a relative risk of 1.7 for smokers. PC risk remains high for up to 10 years after smoking cessation. Risk is seemingly dependent upon dosage, and increases with every five cigarettes daily (9,10).

However, prevalence has changed for some risk factors over the past few decades, including smoking, which was reduced overall, particularly in males, but increased in women. This all leads to a greater increase in cancer incidence among women, partly because of a higher smoking rate.

There is growing evidence on a relationship between alcohol use and pancreatic cancer. Heavy drinking is linked to chronic pancreatitis, a well-established risk factor for PC (11). Most evidence comes from heavy-drinking populations, with a study reporting a moderate risk increase by 19 % versus non-drinkers or occasional drinkers. Other studies have shown smaller, non-statistically significant increases in heavy drinkers. Risk seems to be greater in males, but data are conflicting (12). No differences exist according to type of alcoholic beverage, albeit some prospective studies have reported a greater risk for liquors when compared to other types (13).

In contrast there is a marked increase in obesity incidence and prevalence. According to the European Survey of Health in Spain for 2020, 44.9 % of males and 30.6 % of

females are overweight, and 16.5 % of males and 15.5 % of females have obesity (14). Obesity has been associated with increased PC incidence. The 2012 World Cancer Research Foundation Panel directly associated body mass, abdominal circumference, and body weight increases with PC (15). BMI increases are associated with consistent increases in PC risk (16).

Diet components, as environmental risk factors for PC, seem less influential than initially posited by population-based studies. Some studies demonstrate that higher red or processed meat consumption may moderately increase PC risk (17). There is limited evidence from case-control studies supporting a protective effect of fruit and vegetable intake on PC risk (18).

Diabetes mellitus is associated with increased PC risk (16). Chronic diabetes (for over 10 years) has been associated with increased PC risk. A cohort analysis showed that PC risk increased eightfold versus patients without diabetes mellitus (19). At PC diagnosis, 25 % of patients have diabetes and 40 % have prediabetic elevations of glycemia (20). However, a causal relationship between diabetes and tumor induction has not been well established (21).

This analysis should prompt reflection and help us develop new legal measures for health promotion and modifiable risk factor prevention through fostering physical exercise, healthy nutrition, and Mediterranean diet, and avoiding smoking as well as alcohol, red meat, and animal fat consumption. In this regard reducing VAT for Mediterranean diet components, overtaxing tobacco, alcohol, refined sugars and saturated fats, and promoting exercise by building bikeways, pedestrian areas and sports centers, or by promoting public transportation, represent instruments within the reach of public administrations to prevent risk factors for cardiometabolic disease and multiple malignancies, including pancreatic cancer (22-24).

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