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OTHERS

Young-Onset Pancreatobiliary Cancers—Whereto from Here?

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Abstract
This Invited Editorial towards the Special Issue on Hepatobiliary and Pancreatic Surgery highlights the global problem of young-onset cancers. The paucity of data on young-onset pancreatobiliary cancers is presented in the context of its relevance to India (and its large component of adults in the at-risk age group for these cancers). In the face of limited information on the underlying cause of young-onset cancers, the author draws attention to evidence from colorectal cancer. The readers are encouraged to develop collaborative efforts in India to address answers to much needed questions on the management of young-onset pancreatobiliary cancers, some of which are listed in this Editorial.

Keywords Outcomes · Survival · Genetics · Epigenetics

Globally, there has been an increase in reports of young-onset cancers affecting gastrointestinal organs, especially the colon and rectum, over the last few years [1]. Interestingly, this phenomenon of cancers affecting individuals younger than 40–50 years of age, in the absence of known hereditary cancer syndromes, was reported from India more than 2 decades ago. Professors Mohandas and Desai reported, and I quote, "high rates of rectal cancers in young Indians could suggest a different etiopathogenesis, which is neither inherited nor traditional diet-related" [2]. Deng opined that India and China were probably the first to notice the disturbing rise in young-onset rectal cancers owing to their large populations. The predominant composition of individuals in the reproductive age-group quite likely amplified this effect. Undeniably, reports of young-onset colorectal cancer dominate the publication in this space. So, what about pancreatobiliary cancers? When I worked at the Tata Memorial Centre in Mumbai, I was always intrigued that the median age group of surgically resected pancreatic and gallbladder cancer patients were consistently a decade lower than reported from the USA [3, 4]. In fact, this finding was consistent across the major Indian pancreatic cancer surgery centres at the time [5]. However, it was not just the cohort of surgically resected patients. In a hospital-based cohort, the mean age of patients presenting across all stages of gallbladder cancer was 51.2 years [6]. Most Indian Hepato-Pancreato-Biliary (HPB) cancer surgeons practicing in high-volume centres will attest to this disturbing trend of a high number of young females presenting with gallbladder cancer [7].

Recently, we interrogated the South-Australian Cancer Registry data over the last 3 decades, and reported that there has been a steady increase in the incidence of pancreatic adenocarcinoma amongst individuals less than 50 years of age [8]. Ansari et al. [9], too, reported similar findings from the USA. However, when I performed a PubMed search using the terms "gallbladder cancer" and "young-onset" (dated 5th July 2022), I was disappointed to note that the search yielded 0 results. The other issue with young-onset cancers is the associated poor survival. Pancreatic [10] and gallbladder [11] cancer are inherently notorious for their low overall survival. However, patients with young-onset disease have a lower survival than even their older counterparts [8, 9]. Ben-Aharon et al. [12] demonstrated variations in the genomic landscape of pancreatic ductal adenocarcinoma between the early- and late-onset cohorts. The evidence, thus, points to young-onset disease being clinically different likely due to an underlying difference in tumour biology. This disturbing realisation led me to the obvious question, "what are we doing about it?".

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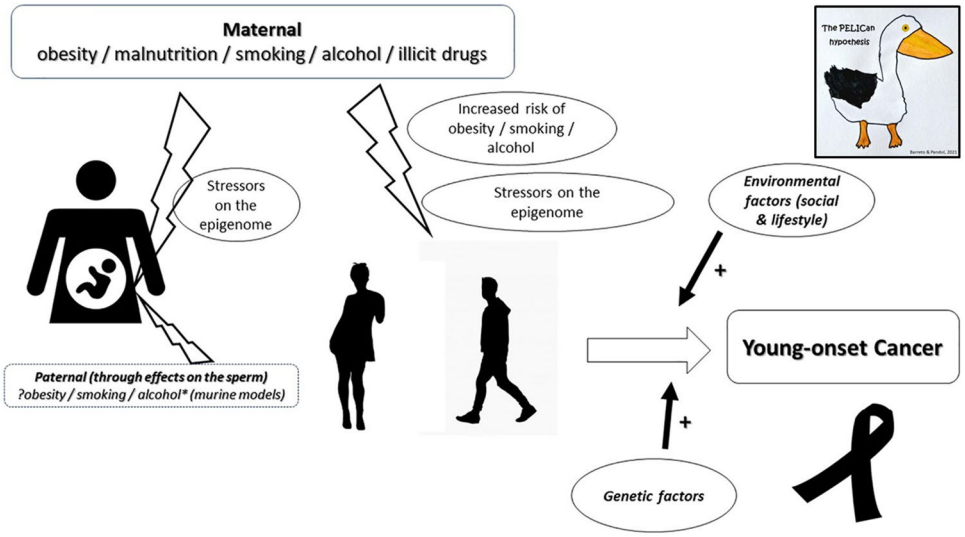

Fig. 1 The PELICan hypothesis (*reproduced from Barreto and Pandol. Front Oncol 2021;11:653289; covered under CC-BY licence*) with the hypothesis logo (*inset*)

Based on the relatively higher incidence of colorectal cancer in the world compared to pancreatobiliary cancer, the reports of the impact of underlying tumour biology on treatment response have emerged in young-onset colorectal cancer. Given the relative paucity of the same information in pancreatobiliary cancers, we could learn from the experience of our colorectal colleagues. Fontana et al. [13] used individual patient data from six trials in the International Duration Evaluation of Adjuvant (IDEA) Chemotherapy database to compare clinical characteristics, treatment adherence, adverse events, and outcomes of patients with early-, versus late, -onset colorectal cancer. While patients with early-onset cancer had a better performance status, similar tumour (T) stage, higher nodal (N2) disease rate, were more likely to complete their planned treatment, and received a higher treatment dose intensity, they experienced recurrences more frequently than the late-onset cohort. The early-onset cohort also had a higher cancer-specific mortality rate (for those in the high-risk stage III). In 2014, we had reported this lower disease-specific survival rates in early-onset rectal cancer patients from India using a stage-matched comparison [14].

The accumulating evidence, thus, leads us to posit a provocative question—"Are we justified in treating early- and late-onset cancers using the same drugs and regimens?" In the absence of evidence to respond to this question with conviction, we need to act now! There is need for prominent organisations such as the Indian Council of Medical Research to define the road map to address the problem. Another avenue is for the high-volume HPB centres, under the auspices of the Indian Chapter of the International Hepato-Pancreato-Biliary Association, to collaborate to develop a National registry on young-onset pancreatobiliary cancers across all stages of the disease. There are important questions that need to be answered, such as:

a) How do we best manage these patients? Are the existing treatment algorithms, developed from treating late-onset cancers, effective in the young- or early-onset cohort? Is the difference in tolerability and response to FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin) between the young and older patients with pancreatic cancer a reflection of tumour biology, rather than merely an age-related phenomenon?
b) Should we treat all young-onset pancreatobiliary cancer patients with neoadjuvant therapy even for resectable disease given their poorer overall survival?
c) In a study published a few years ago based on the experience treating gallbladder cancer patients [4], I noted early failures (at 18 months onward) despite complete (R0) resections. Thus, would young-onset gallbladder cancer patients benefit from metronomic [15] chemotherapy?

Professor V. K. Kapoor referred to gallbladder cancer as an Indian disease [16]. It has been postulated that early life exposure to antibiotics, the ever-spreading obesity pandemic, cigarette smoke, alterations in the gut microbiome, and in mismatch repair genes, with resultant microsatellite instability are some factors postulated to play a role in young-onset carcinogenesis [17, 18]. In the PELICan hypothesis, we suggested that the risk of young-onset cancer begins in the perinatal period following foetal exposure to stressors, including maternal malnutrition, smoking, or alcohol, with the consequent triggering of epigenomic events aimed at helping the foetus cope/adapt to these stressors. Exposure to the same stressors, early in that individual's life, reactivates these "responses designed to be protective" but ultimately resulting in a loss of regulation at a metabolic and/or genetic level culminating in neoplastic evolution (Fig. 1) `[19]. The foundations of the hypothesis [19] could explain why the

problem of young-onset carcinogenesis is more likely to be encountered in developing and industrialised countries. Thus, it is up to us to investigate this problem that threatens our young and middle-aged population. Only in doing so can we determine the appropriate therapy for these patients, as well as predict cancer behaviour and treatment response, with the overarching aim of improving not only disease-specific survival, but overall survival, without compromising quality of life.

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Declarations

Research Involving Human Participants and/or Animals Not applicable.

Informed Consent Not applicable.

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