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## Stromal inflammation, fibrosis and cancer: An old intuition with promising potential

Oliver Oey, Angela Felicia Sunjaya, Yasir Khan, Andrew Redfern

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### Abstract

It is now well established that the biology of cancer is influenced by not only malignant cells but also other components of the tumour microenvironment. Chronic inflammation and fibrosis have long been postulated to be involved in carcinogenesis. Chronic inflammation can promote tumorigenesis *via* growth factor/cytokine-mediated cellular proliferation, apoptotic resistance, immunosuppression; and free-radical-induced oxidative deoxyribonucleic acid damage. Fibrosis could cause a perturbation in the dynamics of the tumour microenvironment, potentially damaging the genome surveillance machinery of normal epithelial cells. In this review, we will provide an in-depth discussion of various diseases characterised by inflammation and fibrosis that have been associated with an increased risk of malignancy. In particular, we will present a comprehensive overview of the impact of alterations in stromal composition on tumorigenesis, induced as a consequence of inflammation and/or fibrosis. Strategies including the application of various therapeutic agents with stromal manipulation potential and targeted cancer screening for certain inflammatory diseases which can reduce the risk of cancer will also be discussed.

**Key Words:** Inflammation; Fibrosis; Tumour microenvironment; Stroma; Cancer



**Core Tip:** Chronic inflammation and fibrosis have long been postulated to be involved in carcinogenesis *via* numerous mechanisms including but not limited to growth factor/cytokine-mediated cellular proliferation, apoptotic resistance, immunosuppression; and free-radical-induced oxidative deoxyribonucleic acid damage. In this review, we discuss various inflammatory and/or fibrotic conditions that have been associated with increased cancer risk, with particular emphasis on their pathophysiology. We also review various therapeutic agents and specific cancer screening that could be applicable in reducing the incidence of cancers developing from the corresponding inflammatory and/or fibrotic conditions, thereby reducing morbidity and mortality.

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## INTRODUCTION

In recent years, there is growing consensus that the biology of cancer is not solely defined by malignant cells, but also by the surrounding tumour microenvironment (TME). The TME consists of cellular and non-cellular stroma. The concept that the TME may influence cancer biology was inspired by the observation of immune cells surrounding the tumour by Rudolf Virchow in 1863, and “the seed and soil theory” by Stephen Paget in 1889, in which he hypothesised that the metastatic destination of a certain cancer is dependent on similarities between the TME of primary tumour and the microenvironment at the site of metastases[1,2]. Since then, there have been significant advancements in the understanding of the impact of the TME on the behaviour of malignant cells, from initial tumorigenesis, through progression to therapy resistance[3-5]. This review will focus on the impact of both the physiological and pathological tissue microenvironment, particularly stromal fibrosis and inflammation, on tumorigenesis.

In this context, stroma refers to the component of an organ which provides biomechanical and nutritional support to the corresponding parenchyma. Specifically, it comprises of immune cells, fibroblasts, mesenchymal stromal cells, endothelial cells, pericytes, adipocytes, and the extracellular matrix (ECM). The ECM, consisting of collagen, proteoglycans, glycosaminoglycans and other macromolecules, provides structural and biochemical support for cellular components in the surrounding parenchyma. Of note, some authors do not include immune cells as a component of stroma, however, immune cells such as macrophages, neutrophils and lymphocytes, play an integral role to the function of parenchymal cells and can have far-reaching effects on tumour biology and consequent behaviour, as such they will be classified as a stromal component in this review.

Many stromal components have been shown through various *in vitro* and animal studies to influence the behaviour and fate of normal cells, including altering the risk of malignant transformation[6-8]. Inflammation and fibrosis are both common processes that significantly alter the cellular and ECM components of normal stroma and so may influence or underlie such behavioural shifts. Both processes have been seen to upregulate the expression of several tumorigenic signalling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), signal transducers and activators of transcription (STAT), wntless-related integration site (Wnt) and phosphatidylinositol 3-kinase (PI3K) *via* the release of pro inflammatory cytokines[9-12]. Hence, several inflammatory and fibrotic conditions have been linked as triggers for tumour development in the organ involved, whether due to autoimmune responses (inflammatory bowel disease and colorectal cancer[13]), bacterial or viral infections (pneumonia or tuberculosis with lung cancer[14]) and environmental factors (silica and lung cancer[15]).

Often, these pathological processes appear to be required for tumorigenesis rather than simply an overrepresentation of certain otherwise normal stromal components. For instance, inflamed adipose mammary tissue in the context of obese mice, increases myofibroblasts number, promoting fibrosis and transformation of normal to malignant breast tissue[6], whereas normal mouse fibroblasts have been shown to prevent clonal proliferation of polyoma virus-transformed cells *in vitro*[7]. However, there are less frequent precedents where normal stromal components may also contribute to tumorigenesis. Normal fibroblasts have been demonstrated to promote the generation of breast cancer stem cells[8]. Additionally, high mammographic breast density, which results from a higher density of stromal and glandular breast components and a lower proportion of adipocytes, is a potent risk factor for breast cancer development.

In this review we will discuss various medical conditions substantively characterised by inflammation and fibrosis, specifically those known to be linked to increased cancer risk. Furthermore, we will look to whether scenarios exist where physiological variations in stromal composition correlate with differing cancer incidence. In doing so, we will discuss the biological contribution of the various stromal components to tumorigenesis known to date and discuss interventions that may influence these processes to achieve therapeutic advantage.



## **PATHOLOGICAL INFLAMMATION, FIBROSIS AND CANCER RISK**

A range of medical conditions exist that involve one or both of these processes. A common evolution pathogenically is of initial inflammation with subsequent fibrosis. However, each of the processes may occur in isolation. Here we look across a range of scenarios at whether each may affect cancer risk in isolation or whether both appear to be required for tumorigenesis (Table 1).

## **INFLAMMATORY BOWEL DISEASE AND COLORECTAL CANCER**

Inflammatory bowel disease (IBD) is sub-divided into ulcerative colitis (UC), which affects only the large bowel, and Crohn's disease (CD) which can involve any area of the gut from mouth to rectum[16]. The risk of developing colorectal cancer in UC patients is elevated compared to the disease-free population, with an overall risk of 4.8[13]. Similarly, in CD risk is elevated although to a more moderate degree, by 2-3 times[17]. In keeping with the small bowel involvement in CD, small intestinal tumours are also increased, by a relative risk of 18.75%[17]. The risk in both conditions is associated with duration and extent of inflammation[18]. Beyond inflammation, both conditions can also result in fibrosis although the pattern differs. Fibrosis leading to eventual stricture and potential obstruction is more common in CD than UC, with around 25% of CD sufferers eventually destined to develop a stricture over the course of the illness[19]. On initial consideration this appears at odds with the risk of colorectal cancer, but may be explained by the distribution of fibrotic change. In UC fibrosis is often superficial, affecting only the mucosal and sub-mucosal layers[20] but still, therefore, able to impact the epithelial layer from which neoplasms arise, and generally impacting a longer continuous length of colon. In contrast, Crohn's disease is characterized by patchy change and skip lesions such that the total area of involved epithelium is often less[16].

Considering these patterns and parallel links in other organs between inflammation, fibrosis and neoplastic transformation, the development of colitis-associated carcinoma (CAC) appears highly likely to be directly attributable to chronic inflammation and consequent fibrosis[21,22]. There is a biological rationale, with previous studies showing that certain inflammatory cytokines prominent in UC, namely TNF- $\alpha$ , IL-6 and TGF- $\beta$  can promote a pro-tumorigenic microenvironment by stimulating essential cancer stem cell pathways, evading growth suppressors, and resisting apoptosis[23-25]. This occurs *via* induction of various molecular signalling pathways including NF- $\kappa$ B[9], STAT[26] and Wnt pathways[27]. Incidentally, these cytokines can also promote fibrosis. TNF- $\alpha$  has been demonstrated to induce IL-6 production, which is partly responsible for proliferation of fibroblasts[28,29]. In addition, TGF- $\beta$ , highly expressed in intestinal epithelial cells, inflammatory cells and fibroblasts is known to induce fibrogenesis and ultimately the deposition of ECM such as collagen, *via* the Wnt/ $\beta$ -catenin pathway, which is also often activated early in dysplastic and surrounding non-dysplastic intestinal epithelial cells, in the setting of CAC carcinogenesis[10,30,31]. This concurs with the upregulation of type 1 collagen, revealed by proteomic analysis in the early stages of colorectal carcinogenesis[32]. Whether or not collagen promotes CAC carcinogenesis remains ambiguous, however increase in collagen may disrupt the polarity of healthy intestinal epithelial cells and stimulate cellular proliferation, thereby promoting malignant transformation.

While it is generally understood that fibrosis occurs as a result of chronic inflammation, it is now understood that fibrosis in IBD may occur without inflammation[33], and further that not all people with IBD develop fibrosis[34]. This prompts the question as to whether either fibrosis or inflammation without the companion process can also trigger carcinogenesis – a question which remains unanswered today due to a lack of cohorts with data that allow the linking degrees of inflammation and fibrosis to cancer risk.

## **CHRONIC PANCREATITIS AND PANCREATIC DUCTAL ADENOCARCINOMA**

Chronic pancreatitis (CP) is a major risk factor for the development of pancreatic ductal adenocarcinoma (PDAC), increasing the risk of PDAC by 20-fold relative to disease-free population[35]. Both CP and PDAC share a common pathological feature – abundant desmoplastic and inflammatory stroma[36]. Hence, the link between the former and the latter could be attributed to the events occurring in the surrounding inflammatory milieu. This was proven in an animal study involving the insertion of K-ras oncogenes within the endogenous K-ras locus, in which mice without pancreatitis did not develop PDAC, while those with pancreatitis did[37]. Thus, it could be deduced that inflammation is a critical factor in PDAC carcinogenesis, at least in response to this, the commonest of oncogenes implicated in pancreatic cancer. In chronic pancreatitis, the release of inflammatory cytokines such as TNF- $\alpha$  and TGF- $\beta$  and growth factors such as vascular endothelial growth factor (VEGF) and PDGF trigger the proliferation of fibroblasts and the activation of pancreatic stellate cells (PSC) towards a more myofibroblast-like phenotype[38,39]. Activated PSC have a number of functions, including sustaining proliferative signalling in pancreatic epithelial cells; the release of growth factors; and the synthesis of ECM proteins, notably collagen, fibronectin and laminin[40,41]. The deposition of various ECM proteins could cause a perturbation in the dynamics of the ECM, potentially damaging the genome surveillance machinery of normal epithelial cells. Supportive of a role for certain ECM components in PDAC progression is the finding that collagen 1, 4 and hyaluronic acid which promotes cell survival, proliferation and invasion, with higher levels associated with reduced survival[42-44]. This is further supported by the therapeutic benefit derived from the administration of PEGylated Recombinant Human Hyaluronidase in addition to chemotherapy in PDAC patients[45,46].



Table 1 Summary of various inflammatory and fibrotic conditions and relevant malignancies

Disease	Associated cancer	Mechanism	Risk ratio	Possible therapeutic targets
Inflammatory bowel disease	Colorectal cancer	Increased pro-inflammatory cytokines (TNF- $\alpha$ , IL-6 and TGF- $\beta$ )[24,30,34]; Increased signalling of pro-tumorigenic molecular pathways, apoptosis resistance, fibrogenesis (NF- $\kappa$ B and Wnt/ $\beta$ -catenin)[9,27,30,34]	Ulcerative colitis – 4.8-fold increase[13]; Crohn's disease – 2-3-fold increase[17]	Thiopurines[173] and anti-inflammatory such as mesalazine [174] and NSAID[149]
Chronic pancreatitis	Pancreatic ductal adenocarcinoma	Increased cytokines (TNF- $\alpha$ and TGF- $\beta$ ), growth factors (VEGF, PDGF)[38]; Fibroblast and pancreatic epithelial cell proliferation[40]; Activation of pancreatic stellate cells [39,40]; Increased ECM protein (collagen 1 and 4, laminin, fibronectin) and hyaluronic acid deposition[38]	20-fold increase[35]	PEGylated Recombinant Human Hyaluronidase[45,46]; NSAID[149]
Idiopathic pulmonary fibrosis	Lung cancer	Cellular morphological abnormalities (metaplasia, dysplasia) in fibrotic areas[59]; Reduced immune expression (monocytes, lymphocytes, macrophages) in fibrotic areas[50]; Mutations in tumour-suppressor genes [54]; Upregulated gene expression of ECM components such as collagen and MMP (MMP9 and 11)[57]	3.5-7.3 fold increase [51]	Anti-fibrotic drugs (pirfenidone and nintedanib)[175]
Pneumoconiosis	Lung cancer	Silicosis: Chronic increased release of pro-inflammatory cytokines (IL-12, IL-23 and TNF $\alpha$ ) results in DNA damage [66]; Immunosuppression through increased expression of inhibitory immune markers (PD-1, LAG3, FOXP3)[70]. Asbestosis: Increased inflammation (IL-1 $\beta$ , TGF- $\beta$ and PDGF) and fibrosis through expression of NLRP3[70]; Increased ROS and RNS[64,68]; Increased expression of proliferation signalling pathways (EGFR-ERK)[73]	Silicosis – 3-fold increase[15]; Asbestosis – 1.5-6.8-fold increase[65,65]	Anti-fibrotic drugs (pirfenidone and nintedanib)[152]
TB	Lung cancer	Upregulation of anti-apoptotic protein expression <i>via</i> inflammatory cytokines (TNF- $\alpha$ and IL-6)[59,76,78]	Pneumonia – 1.4-fold increase[14]; TB – 1.9-fold increase[14]	NSAID[176]
Liver cirrhosis	Hepato-cellular carcinoma	Cellular proliferation, telomere shortening <i>via</i> inflammatory cytokines (TGF- $\beta$ , TNF- $\alpha$ and interleukins)[83,84]; Genomic instability (p53, Ras, mTOR, Wnt signalling pathways)[11,84]; Reduced expression of CD4+ and CD8+ cytotoxic T cell[85]; Increased regulatory T-cell response [86]; Activation of hepatic stellate cells increase myofibroblast and ECM production[11,87]; Hypoxia in fibrosis leads to genotoxicity (ROS, RNO) and angiogenesis (VEGF)[92]	Hepatitis B related – 1.17-fold increase [81]; Hepatitis C related – 1.15-fold increase[81]; NAFLD-related – 1.6-23.7-fold increase[161]	LOX/LOXL2 inhibitors[161,162]; NSAID, Pentoxifylline [177,178]
Primary biliary cholangitis	Cholangiocarcinoma	Increased proliferative signalling <i>via</i> inflammatory cytokines (IL-1 $\beta$ , IL-6 and HGF)[96-98]; IL-6 activates p38-MAPK, increases DNA methyltransferase (DNMT) Mcl-1 and telomerase expression[96]; DNA damage (BRAF, K-ras, cyclin d-1, c-myc, COX-2 and p53) due to dysregulated NO production[98]; Fibroblast proliferation and ECM production (collagen type 1 and 3)[103]	9-fold increase[94]	Natural anti-inflammatory products (Curcumin)[102]
GERD and Barrett's oesophagus	Oesophageal cancer	Increased inflammatory cell recruitment (macrophages T, B, dendritic cells)[107]; Inflammatory cytokine release (TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-8) activates pro tumorigenic signalling pathways (NF-Kb, STAT-3, HIF-1a)[107,108]; Reduced immune response due to immunosuppressive cytokines (IL-10)[112]; Oxidative stress (ROS and RNS) induce mutagenesis of oncogenes and tumor suppressor genes[110]	30-125-fold increase [106]	NSAID[149]
OSF	Oral squamous cell carcinoma	Increased inflammatory cell recruitment[118]; Oxidative stress induces p53 mutation, decreased DMNT and increased HSP70 and MDM2-P2 promoter[120,122]; Increased prostaglandins, cytokines and growth factors (IL-6, TNF- $\alpha$ , PDGF and TGF- $\beta$ )[118,119]; Fibrogenesis <i>via</i> IL-6 and TGF- $\beta$ leads to increased ECM protein production (collagen, fibonectin) and inhibit ECM breakdown (PAI-1, TIMP)[124,125]; OSF-associated fibroblast promote dysplastic keratinocyte proliferation <i>via</i> GRO- $\alpha$ release and EGFR/ERK activation[128]	19-fold increase[114]	Anti-oxidants, steroids and hyaluronidase [178]
Physiological breast stromal density, breast conditions – chronic mastitis, sclerosing adenosis	Breast cancer	Mammographically dense breast have higher ECM proportion (collagen, immune cells)[131,133]; Mammographically dense breast have higher proportion of glandular epithelial components and lower proportion of adipocytes[132-134]	Physiological higher MBD: 4-6-fold increase[130]; Chronic mastitis: 3-fold increase[137]; Sclerosing adenosis: 2-fold increase[138]	Anti-estrogens (tamoxifen, raloxifene, exemestane and anastrozole)[154-157]; NSAID[149]; LOX-like inhibitors[159,160,163]



GERD: Gastroesophageal reflux disease; OSF: Oral submucosal fibrosis; TNF- $\alpha$ : Tumor necrosis factor-alpha; TGF- $\beta$ : Transforming growth factor beta; NF- $\kappa$ B: Nuclear factor  $\kappa$ B; VEGF: Vascular endothelial growth factor; NSAID: Anti-inflammatory; GRO- $\alpha$ : Regulated oncogene- $\alpha$ ; MBD: Mammographic breast density; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; TB: Tuberculosis; ECM: Extracellular matrix; PDGF: Platelet-derived growth factor; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; HGF: Hepatocyte growth factor; NO: Nitric oxide; BRAF: Proto oncogene B-Raf or v-raf murine sarcoma viral oncogene homolog B1; COX-2: Cyclooxygenase-2; NAFLD: Non alcoholic fatty liver disease.

However, certain alterations in the ECM can be tumour-inhibitory rather than promoting. Quantitative analysis of stroma density in PDAC samples from patients' autopsy revealed that tissue stroma density was substantially lower in samples from patients with metastatic PDAC and that higher stromal content was associated with a more favourable outcome[47]. This finding was further supported by Rhim *et al*[48] who demonstrated that diminished stromal density induced by knocking out sonic hedgehog in an established PDAC mouse model significantly enhanced tumour vascularity and proliferation. Furthermore, another study by Erkan *et al*[49] in which resected PDAC tumors were analysed for PSC activity and collagen deposition showed that the combination of high collagen deposition and low stromal activity was associated with a better prognosis than low collagen deposition and high stromal activity. While these studies relate to the effect of stroma on tumour progression/regression, considering the similarities between carcinogenesis and organ development, it is likely that these findings apply to PDAC carcinogenesis. Combining findings from these studies, the role of chronic inflammation and fibrosis in influencing PDAC risk remains ambiguous.

## INTERSTITIAL LUNG DISEASE AND LUNG CANCER

Idiopathic pulmonary fibrosis (IPF) is the most common subtype of interstitial lung disease which is characterised by aberrant accumulation of fibrotic tissue in the lung parenchyma[50]. While the pathophysiology of IPF remains to be fully elucidated, the disease is thought to be mainly fibrosis-driven with minimal involvement of inflammation cascade[50]. Over the past decade, many studies have shown that IPF is linked to development of lung cancer, with a relative risk of 3.5-7.3 compared to healthy population[51]. One of the main reasons for this association is that IPF and lung cancer could have similarities in their pathophysiology, in terms of cellular morphological anomalies, dysregulated cytokine signalling and genetic mutations[52]. A study by Kawasaki *et al*[53] established that morphological aberrations in the lung epithelial layer, ranging from metaplasia and dysplasia to carcinoma, have been identified in fibrotic lung regions of IPF patients. This could be related to microsatellite instability and loss of heterozygosity, including mutations in tumour-suppressor genes such as fragile histidine triad gene, that are present at higher frequency in lung epithelial cells of IPF patients relative to healthy population[54,55]. Genetic alterations like these could be attributed to fibrosis, mainly mediated by TGF- $\beta$  released by various immune cells, and other changes in the stroma in IPF patients[56]. Using publicly available datasets, Saito *et al*[57] confirmed that 10% of the genes upregulated in lung cancer stroma, which include those coding for ECM components, mainly collagen (COL1A2, COL3A1, and COL5A2), and matrix metalloproteinases (MMP9 and 11), are also elevated in IPF. Furthermore, while increased immune cell infiltrates releasing cytokines, which promote epithelial proliferation and resist apoptosis are noted in the early stages of IPF, reduced number of lymphocytes, macrophages and monocytes were reported in fibrotic-predominant areas compared to epithelial-predominant ones in the later stages[57-61]. This implies that lung epithelial cells undergoing malignant transformation in the former are more likely to evade immune surveillance and progress to invasive malignancies in the latter. This observation concurs with the fact that lung cancers associated with IPF tend to develop in the peripheral and lower lobes – the fibrotic-predominant regions[62].

While IPF is mainly driven by fibrosis, other subtypes of ILD such as pneumoconiosis involve an inflammatory-driven condition that has been associated with lung cancer[50,63,64]. Patients with silicosis and asbestosis are about 3 times and 1.5 times more likely to develop lung cancer than the general population[15,65]. Chronic inflammation triggered as a result of the continuous activation of macrophages in an attempt to clear the silica particles is thought to mediate lung carcinogenesis in patients with silicosis[63]. Consequently, there is massive release of cytokines such as IL-12, IL-23, and TNF $\alpha$  which place lung epithelial cells at an increased risk of DNA damage and thus their susceptibility to malignant transformation[66]. This is demonstrated unequivocally by Wang *et al*[66] in Gprc5a-knockout mice exposed to silica where neoplastic epithelial cells were found in areas of intense lung damage and fibrosis which were thought to be a consequence of chronic inflammation. Furthermore, Freire *et al*[67] demonstrated increased lung adenocarcinomas in mice treated with the combination of the carcinogen N-nitrosodimethylamine and silica. On histopathological analysis, there was increased expression of various inhibitory immune markers including programmed cell death protein 1, lymphocyte-activation gene 3, and forkhead box P3, as well as the presence of regulatory T cells in mice treated with NMDA and silica compared to silica alone[67]. This produces marked immunosuppression which increases the risk of carcinogenesis, providing another plausible explanation for the link between silicosis and lung cancer.

Similarly, in the case of asbestosis – linked with a 6.8-times and increased incidence of lung cancer respectively compared with the general population – the pathogenesis by which it causes malignancy appears to be a combination of inflammation and the direct genotoxic effect of asbestos fibres on the genome[68,69]. Alveolar macrophages have been known to play a major role in handling asbestosis fibres[68]. The entrapment of asbestos stimulates the activation of NOD-like receptor family, the pyrin domain containing 3 expressed in alveolar macrophages which promotes the activation of IL-1 $\beta$ , along with other cytokines such as TGF- $\beta$  and PDGF which are responsible for the formation of



fibrotic nodules[68,70]. In addition, macrophages increase the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby stimulating genotoxicity, chronic inflammation and thus malignancy transformation[71]. More specifically, numerous studies have demonstrated that chronic inflammation as a result of asbestos exposure affected several cell signalling pathways that are likely responsible for the development of lung cancer including the epidermal growth factor receptor (EGFR)-related extracellular signal-regulated kinase (ERK) signaling that promote lung epithelial cell and fibroblast proliferation[71-73]. While these studies have established the effect of chronic inflammation on development of lung cancer and mesothelioma, there is still a need to ascertain the relevance of fibrosis and lung cancer *in vivo*.

## PNEUMONIA, TUBERCULOSIS AND LUNG CANCER

Infections of the lung have been previously linked with the future development of lung cancer. A meta-analysis by Brenner *et al*[14] demonstrated that pneumonia and tuberculosis was linked with a 1.4- and 1.9-times increased risk of developing lung cancer in the future. While both pneumonia and tuberculosis constitute as infection of the lung parenchyma, the degree of pulmonary inflammation and subsequent fibrosis likely explains the variation in the risk of developing lung cancer[14]. In regards to the former, pulmonary inflammation occurs for a shorter duration and thus the resulting fibrosis is less if not negligible compared to the latter, where a significant level of inflammation and fibrosis is involved[74,75]. Furthermore, in the setting of further tuberculosis (TB) recurrences which can occur in up to 47% of TB patients, repeated inflammatory response will increase the risk of lung cancer each time, with high cumulative risk associated with more frequent recurrences[76,77]. The mechanism by which inflammation increases cancer risk relates to the action of ROS and RNS produced by immune cells on the genome of lung epithelial cells and the ability of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 to upregulate the expression of anti-apoptotic proteins[76,78]. Additionally, recurrent bouts of inflammation results in fibrosis in the surrounding lung parenchyma, which increases the risk of cancer associated with poor lymph drainage[79]. Further supporting the link between inflammation and lung cancer risk is a meta-analysis by Khuder *et al*[80] which demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) conferred a protective benefit in reducing lung cancer risk following adjustment for smoking (OR: 0.68; 95% CI: 0.55-0.85). These studies reaffirm the association between inflammation, fibrosis and lung cancer risk.

## LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

The link between hepatic cirrhosis and hepatocellular carcinoma (HCC) is well-established, with the 5-year HCC cumulative risk of 17% and 15% respectively for hepatitis B-related and hepatitis C-related cirrhosis respectively[81]. NAFLD-related cirrhosis is also associated with the development of HCC, with multi-centre cohort studies showing 1.6 to 23.7 times increased risk[82]. Chronic inflammation and fibrosis are thought to be the major mechanisms explaining this association. In chronic hepatitis, a multitude of immune cells release various cytokines, most notably, TGF- $\beta$ , TNF- $\alpha$  and interleukins, which lead to an increase in cellular proliferation, telomere shortening and genomic instability involving signalling pathways such as mechanistic target of rapamycin and Wnt signalling[83,84]. Additionally, previous studies revealed that CD4<sup>+</sup> cells – involved in activation of the tumour-killing CD8<sup>+</sup> cytotoxic T cells – and regulatory T cells – responsible for suppressing immune response – are diminished and increased respectively in cirrhosis[85,86]. Furthermore, chronic inflammation leads to fibrosis. Specifically, TGF- $\beta$  released by Kupffer cells (macrophages) promote the activation of quiescent hepatic stellate cells (HSCs), analogous to PSCs in the pancreas, becoming myofibroblasts which are the primary source of ECM proteins including collagen, undulin, fibronectin and elastin[11,87]. More recently, others have identified additional cytokines, growth factors and lipid signals produced by other stromal components including endothelial cells, Kupffer cells and adipocytes are involved in HSC activation[88-90]. Fibrosis impairs the hepatic vasculature and produces a hypoxic environment, triggering the production of reactive oxygen, nitrogen species (ROS and RNO). ROS and RNO in turn can cause oxidative DNA damage among hepatocytes, predisposing them to malignant transformation[91]. Additionally, hypoxia induces the transcription of pro-angiogenic factors such as VEGF which is responsible for angiogenesis[92]. Further exacerbating this tumorigenic environment, neo-angiogenesis promotes the recruitment of immune cells like macrophages which results in further inflammation driving a vicious cycle. Today, the relationship between cirrhosis and HCC is extremely robust, that liver stiffness, a hallmark of hepatic cirrhosis is being studied as a means of assessing HCC risk[93].

## PRIMARY BILIARY CHOLANGITIS AND CHOLANGIOCARCINOMA

Primary biliary cholangitis (PBC) is one of the most common risk factors for cholangiocarcinoma, with ninefold increased risk of developing cholangiocarcinoma[94]. The pathogenesis of cholangiocarcinogenesis in patients with PBC is multifactorial. Apart from the biliary constituent in PBC patients, chronic inflammation involving cytokines and growth factors, notably IL-6, hepatocyte growth factor, and IL-1 $\beta$ , released by various stromal and immune cells have been implicated in sustaining proliferative signalling in biliary cells[95-98]. IL-6 is believed to be a predominant contributor in cholangiocarcinogenesis, with the potential to promote cellular proliferation, survival and immortalisation *via* different mechanisms – p38MAPK activation[99], increasing DNA methyltransferase[96], Mcl-1 and telomerase expression[100]. In



addition, the inflammatory milieu in the surrounding bile duct raises the production of NO which increases the probability of DNA damage, affecting genes such as BRAF, K-ras, cyclin d-1, c-myc, COX-2 and p53[98,101]. Using a hamster model of cholangiocarcinoma, Prakobwong *et al*[102] demonstrated a decrease in incidence of cholangiocarcinoma, accompanied by decline in pro-inflammatory, growth signalling and anti-apoptotic protein expression including COX-2, cyclin-d1, c-myc, bcl-2 and bcl-xL following administration of curcumin, traditional anti-inflammatory agent derived from turmeric. This highlights the crucial role of inflammation in cholangiocarcinogenesis. Thirdly, fibrosis, instigated by the release of cytokines like IL-6 and TGF- $\beta$  by immune cells, has also been shown to be involved in the neoplastic transformation of biliary cells. Using a liver cirrhosis mouse model, Farazi *et al*[103] showed that increased levels of fibroblasts along with type 1 and 3 collagen stimulate intrahepatic cholangiocyte proliferation and subsequent malignant transformation in p53-deficient mice. In another study, Ling *et al*[104] demonstrated that cholangiocarcinoma was induced in a rat model of thioacetamide (TAA)-induced hepatic fibrosis. The association between inflammation, fibrosis and cholangiocarcinogenesis is sufficiently convincing to stimulate interest in agents such as curcumin that may diminish the two are being investigated to reduce the risk of cholangiocarcinoma[102,105].

## GASTROESOPHAGEAL REFLUX DISEASE, BARRETT'S OESOPHAGUS AND OESOPHAGEAL CANCER

For a long time, chronic gastroesophageal reflux disease (GERD) patients have been known to be at risk of oesophageal cancer (OC), with 10%-20% developing Barrett's oesophagus (BO), making them 30-125 times more likely than the general population to develop OC[106]. Unlike HCC and cholangiocarcinoma where fibrosis is thought to be crucial to carcinogenesis, the pathophysiology of OC is inflammation-predominant. In GERD patients, chronic inflammation and oesophageal injury initiated by reflux of gastric acid bile and salt, result in BO, which is an intermediate step to progression to OC. More specifically, reflux promotes the recruitment of inflammatory cells, notably macrophages T, B and dendritic cells which release various pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, IL-1 $\beta$  and IL-8 that are responsible for NF-K $\beta$ , STAT-3, and HIF-1 $\alpha$  activation[12,107,108]. This in turn leads to cellular proliferation and de-differentiation as part of a metaplastic process, a frequent precursor to neoplastic transformation. Further, immunosuppressive cytokines, notably IL-10 are found at higher levels in BO, and thus, could render healthy squamous epithelial cells undergoing malignant transformation less susceptible to destruction as a result of immune surveillance[109]. Furthermore, chronic inflammation creates a state of oxidative stress, evident by the increased levels of ROS and RNS present in BO[110]. The heightened level of oxidative stress in turn induces mutagenesis of oncogenes and tumour-suppressor genes, including TP53, K-ras, FBXW7 and PI3KCA, thereby contributing to OC carcinogenesis[110]. While chronic inflammation contributes significantly to OC carcinogenesis, the role of other aspects of stroma, including fibrosis on OC carcinogenesis remains unexplored. Interestingly, fibrosis is not apparent in BO, hence providing evidence of an inflammatory condition increasing cancer risk without the need for progression to fibrosis. Considering the reverse situation, we can hypothesise regarding the role of fibrosis on carcinogenesis from studies on eosinophilic oesophagitis, where both inflammation and fibrosis are prominent features but were not found to be associated with increased risk of OC[111]. Several mediators appear to be involved in this fibrosis, namely TGF- $\beta$ , Th-2 type cytokines and ROS[112,113]. We could hypothesise that fibrosis may suppress neoplastic transformation in this scenario[111]. At this stage, while chronic inflammation substantially elevates OC cancer risk, fibrosis may have differing context specific effects on OC risk.

## ORAL SUBMUCOSAL FIBROSIS AND ORAL SQUAMOUS CELL CARCINOMA

Apart from tobacco smoking, oral submucosal fibrosis (OSF) is the major risk factor for the development of oral squamous cell carcinoma (OSCC), increasing the likelihood by up to 19-fold compared to a healthy population[114]. The aetiology for OSF has long been established, with increasing incidence attributed to daily consumption of areca nut and betel quid[115,116]. In addition to the carcinogenic potential of constituents of areca nut and betel quid on activating oncogenes and inhibiting tumour-suppressor genes, they are also known to be inflammatory[117]. This promotes the recruitment of immune cells, predominantly, macrophages, T cells and lymphocytes to the oral mucosa, which in turn release ROS, prostaglandins, cytokines and growth factors, notably IL-6, TNF- $\alpha$ , PDGF and TGF- $\beta$ [118]. These biological mediators, present in the surrounding oral squamous epithelium, promote oral squamous cell proliferation and survival [118]. Additionally, ROS promotes oxidative damage and mutagenesis, resulting in p53 mutations, decreased levels of DNA-methyltransferase repair enzyme and upregulated levels of HSP70 and MDM2-P2 promoter, which ultimately lead to neoplastic transformation in areas of OSF[119-123]. Interestingly, some of the aforementioned biological mediators, namely IL-6 and TGF- $\beta$  are significantly involved in fibrogenesis – synthesising ECM proteins like collagen and fibronectin and simultaneously producing plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitor of metallo-protease which inhibit ECM breakdown[124-126]. This produces extensive fibrosis, particularly in the lamina propria, a hallmark feature of OSF. Recently, in an immunohistochemical study involving tissues obtained from patients with normal mucosa and OSF, Gadbaile *et al*[127] demonstrated that Ki67 expression, a marker for cell proliferation, was directly proportional to  $\alpha$ -SMA expression, a marker for myofibroblast formation, potentially highlighting that fibrosis may be directly involved in neoplastic transformation. The effect of fibrosis on malignant transformation of oral squamous epithelial cells is further stressed in an *in-vitro* study by Ye *et al*[128], who showed that growth-regulated oncogene- $\alpha$  from OSF-associated fibroblasts promote dysplastic keratinocyte cell line proliferation *via* activation of the EGFR/ERK signalling pathway. The potential of inflammation and fibrosis in OSF to cause neoplastic transformation to OSCC is regarded as high, justifying the ongoing search for anti-inflammatory and anti-fibrotic agents to suppress these



processes in OSF[76,129].

## BREAST CANCER, PHYSIOLOGICAL MAMMOGRAPHIC DENSITY, PATHOLOGICAL INFLAMMATION AND CANCER RISK

Up to this point the breast appears to be a unique case in considering links between stromal composition and cancer risk. The differentiator is the strong established link between mammographic breast density (MBD), as assessed on mammographic images, which ties to the stromal composition of the normal breast, and breast cancer risk. Women with MBD lying in the highest quartile have a 4-6-fold higher risk of developing breast cancer than those in the lowest quartile [130,131]. Dense tissue has been found to correlate with higher proportions of ECM, particularly collagen[132], immune cells[133] and glandular epithelial components, and lower proportions of adipocytes[134]. As well as promoting initial carcinogenesis, higher mammographic density has been found to correlate with a higher risk of local relapse, a lower rate for complete response to chemotherapy[135] and a higher rate of relapse after treatment in locally advanced tumours [136].

This raises the question as to whether higher 'physiological' tissue stromal density carries higher risks of cancer in other organs, as well as whether pathological inflammatory and fibrotic processes impact cancer risk in the breast. Considering the latter, inflammatory conditions that result in a sustained inflammatory environment in the breast are relatively rare. Chronic mastitis is a condition whereby there is sustained inflammation usually relating to chronic infection. A retrospective cohort study by Chen *et al*[137] revealed that patients aged  $\geq 40$  with a history of mastitis have 3-fold increased risk of developing breast cancer aHR = 3.71, 95%CI = 1.9-7.02) compared to those without a history of mastitis. On the same note, fibrotic condition of the breast such as sclerosing adenosis has also been associated with an approximate doubling of breast cancer risk in a US retrospective cohort[138]. This further highlights the significance of inflammation and fibrosis in influencing cancer risk and emphasises consideration of more rigorous screening for these conditions and therapeutics which could manipulate the stroma and reduce cancer risk.

## STROMAL MANIPULATION TO THERAPEUTIC ADVANTAGE

The abundant evidence for multiple robust links between inflammation, fibrosis and carcinogenesis (Figure 1), as well as the frequently overlapping spectrum of implicated signalling mediators and pathways, suggest that there may be substantial therapeutic benefit to be achieved by detecting and targeting these processes across many cancer types (Table 1).

Knowledge of the links between inflammation and malignancy are widely exploited in the screening of at-risk individuals with a variety of conditions. First there is promise in the assessment of stromal characteristics to predict cancer risk, thereby allowing identification of individuals suitable for screening or for whom screening could be adjusted. For instance, the strong relationship between MBD and breast risk has been described above. Initiatives are already in progress to use MBD levels to tailor screening, both considering the age at which to start screening and the frequency as well as whether other modalities should be considered such as ultrasound or MRI[139,140]. Additionally, robust link between liver cirrhosis and HCC has prompted surveillance quantification of alpha-feto protein and liver as a means to diagnose HCC earlier[141]. Furthermore, there are screening recommendations for patients with BO and IBD to undergo surveillance gastroscopy and colonoscopy to detect the relevant malignancies at early stages[142,143].

Beyond detection, the common mechanisms underlying links between tissue inflammation, fibrosis and malignancy have led to development of a number of strategies to target these underlying processes including the application of therapeutics including anti-proliferatives, anti-inflammatories, anti-estrogens and anti-fibrotics which will be discussed below.

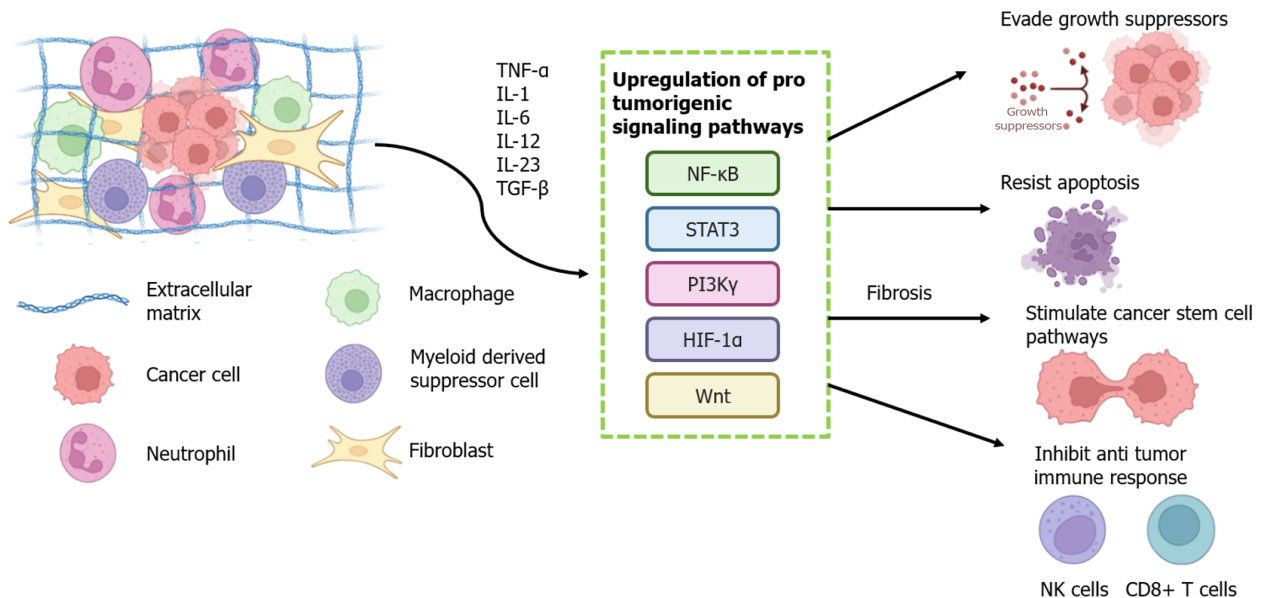
### Anti-proliferative

Thiopurines (azathioprine, mercaptopurine and thioguanine) has been a mainstay drug for IBD patients over the last 50 years. Its main drug effect is derived from the production of its metabolites 6-thioguaninenucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP)[144]. These metabolites exert an immunosuppressive and anti-proliferative effect by binding Ras-related C3 botulinum toxin substrate 1 (Rac1) to thioguanosine triphosphate thus mitigating chronic gut inflammation in IBD. This blockade of Rac1 signalling results in decreased anti-apoptotic protein Bcl-xL expression and subsequent promotion of pro-inflammatory T-cell apoptosis[145,146]. A meta-analysis by Zhu *et al*[147] involving 95397 IBD patients, found that thiopurine use is associated with reduced risk of colorectal neoplasia (case control OR = 0.49, 95%CI: 0.34-0.70; cohort RR = 0.96, 95%CI: 0.94-0.98). While effective as a chemopreventive agent, thiopurine use should be balanced with potential adverse effects such as risk of myelosuppression and in the long term, development of lymphoproliferative disorders[146,148].

### Anti-inflammatory

NSAID used widely in the treatment of chronic pain syndromes have been studied as a chemopreventive agent in a wide range of cancers. NSAIDs reduce inflammation by reversibly and non-selectively inhibiting cyclooxygenase (COX) enzymes which in turn lead to decreased production of prostaglandins and leukotrienes, mediators which have been implicated in carcinogenesis. A meta-analysis by Qiao *et al*[149] comprising of 218 studies demonstrated that aspirin use





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**Figure 1** Schematic showing the links between inflammation, fibrosis and cancer in the tumour microenvironment. NK: Natural killer; HIF-1 $\alpha$ : Hypoxia-inducible factor 1alpha; PI3K: Phosphatidylinositide 3-kinase; STAT3: Signal transducer and activator of transcription 3; NF- $\kappa$ B: Nuclear factor  $\kappa$ B; Wnt: Wingless-related integration site.

was associated with a significant reduction in risk of gastric, esophageal, colorectal, pancreatic, ovarian, endometrial, breast and prostate cancer with rates ranging from 6%-25%. Another meta-analysis investigating the link between NSAID and skin cancer risk has also shown positive results, with significant reduction in risk of developing basal cell carcinoma, squamous cell carcinoma and non-melanoma skin cancer, but not melanoma. Interestingly, no significant chemopreventive effect is observed for COX-2 selective-NSAIDs and NSAID use among European populations[150].

5-aminosalicylates (5-ASA) is a drug class with anti-inflammatory and immunosuppressive properties, generally utilized in treatment of IBD and various rheumatologic conditions which has recently been found to possess chemopreventive properties. It works *via* multifactorial mechanisms but two well-understood mechanisms are the inhibition of prostaglandins and leukotrienes synthesis and scavenging of reactive oxygen species[151]. Previous systematic review of 31 independent observational studies in IBD has demonstrated that 5-ASA use is associated with a 43% reduction in risk of colorectal malignancy among patients with IBD. Of note, the reduction in risk of colorectal malignancy of 50% was more prominent in UC as compared to CD, where the risk reduction was non-significant. Furthermore, the incidence of IBD-related colorectal cancer have significantly declined in recent years and whilst numerous factors could cause this, the role of 5-ASA and other immunomodulatory agents are likely to have contributed to the decrease in cancer incidence[13].

### Anti-fibrotic

Nintedanib and pirfenidone are two anti-fibrotic agents which have been approved for the management of IPF. Both work *via* modulation of fibrogenic growth factors, thereby decreasing fibroblast proliferation, myofibroblast differentiation, collagen and fibronectin synthesis, and extracellular matrix deposition[152]. Recent retrospective study by Naoi *et al*[153] demonstrated that the cumulative incidence of lung cancer in patients with IPF treated with antifibrotic agent was significantly lower than those who were not (2.2% *vs* 4.4% at 1 year, 2.2% *vs* 6.7% at 3 years, and 3.3% *vs* 9.7% at 5 years, respectively;  $P = 0.004$ )[153]. Interestingly, the use of anti-fibrotic agent was also associated with lower lung-cancer related mortality (1.6% *vs* 15.2%, respectively;  $P = 0.0001$ )[153]. With established benefits in terms of slowing progression, possibly improving survival in IPF and more recently, preventing lung cancer development, the use of anti-fibrotic agents should be strongly considered in all IPF patients provided that there are no contraindications.

### Anti-estrogens in breast cancer

Anti-estrogens inhibit the synthesis or antagonise action of estrogen in target organs. Anti-estrogens encompass selective estrogen receptor modulators (SERMs), selective estrogen receptor degrader, aromatase inhibitors, gonadotrophin release hormone agonists and antagonists. Previous studies have shown that tamoxifen, raloxifene, exemestane and anastrozole have significantly reduced the incidence of breast cancer in high-risk women by 49%[154], 76%[155], 65%[156], 49%[157] respectively. Currently, two SERMs, tamoxifen and raloxifene, are approved by the FDA for breast cancer chemoprevention, with anastrozole and exemestane pending approval. The mechanism of action by which antiestrogens prevent breast cancer remains unclear, however, the reduction of breast stromal density brought about by antiestrogen use is thought to confer a less pro-tumorigenic environment and hence lowering breast cancer risk.



## Stromal disruption

Lysyl oxidase (LOX) and LOX-like inhibitors are another drug class targeting the stroma of immense chemopreventive potential. LOXL is amine oxidase which catalyse the cross-linking of collagen and elastin in normal tissue and extracellular matrix, facilitating carcinogenesis, cell proliferation, migration and metastases[158]. Whilst previous studies have mainly investigated LOXL inhibitors as an anti-cancer agent, the preliminary results have been promising and LOX role in carcinogenesis make it a particularly interesting target to prevent carcinogenesis. Anti-GS341, antibody targeting LOXL-2 has been shown to significantly reduce tumour volume and lung metastases in a breast cancer xenograft model using MDA-MB-231 cells into immunocompromised SCID mice[159]. Additionally, an orally bioavailable LOX/LOXL2 inhibitor, CCT365623, developed by Leung *et al*[160] produced significant diminution in tumor growth and metastases in an in vivo model of transgenic LOX-dependent breast tumor mice[160]. These promising preclinical findings have translated to clinical trials exploring LOX/LOXL inhibitor in numerous diseases including myelofibrosis, cirrhosis, and breast cancer[161-164].

Another potential stromal disruption agent targets the extracellular matrix, particularly degradation of hyaluronic acid (HA), an important component of the ECM known to participate in carcinogenesis, tumor progression and metastasis in various cancers[165]. PEGPH20 is a PEGylated human hyaluronidase that showed promise both as single agent or in combination, in numerous preclinical studies[165-167]. Thompson *et al*[168] showed that repetitive PEGPH20 administration significantly inhibited tumor growth by 70% in high-HA prostate PC3 tumors and improved both docetaxel and liposomal doxorubicin activity in PC3 tumors. Additionally, using HA synthase 3-overexpressing and wild-type SKOV3 ovarian cancer model and in the BxPC3 pancreas xenograft tumour model, Morosi *et al*[166] showed that PEGPH20 enhanced the antitumor activity of paclitaxel by modifying the tumour tissue architecture. Despite the promising potential of PEGPH20 in preclinical studies, clinical trials of PEGPH20 in various advanced solid tumours have been disappointing with PEGPH20 failing to meet its primary end point of improvement in overall survival[169]. However, it is crucial to note that PEGPH20 has not been explored in preventing carcinogenesis such as in the context of IBD, cirrhosis and IPF. Considering the significance of the ECM in carcinogenesis, future studies should study the effect of ECM-degrading agents such as PEGPH20 in carcinogenesis.

In addition to targeting the ECM, agents targeting other components of the ECM have been studied. Most notably, agents targeting myofibroblasts which produce pathological fibrosis and thus a pro-carcinogenic environment have shown promising results in previous studies. Depletion of myofibroblasts by targeting its marker, fibroblast activation protein- $\alpha$ , has been shown to inhibit tumor growth by augmenting anti-tumor immunity[170,171]. Additionally, agents targeting TGF- $\beta$ , an important cytokine in myofibroblast activation have also been studied as TGF- $\beta$  inhibition has been demonstrated to prevent myofibroblast activation and prevent immunosuppression and thus cancer progression[172]. Again while these agents are studied as anti-cancer therapies, these drugs have immense potential to be utilised as chemopreventive agents in disorders of chronic inflammation and fibrosis to prevent carcinogenesis.

## CONCLUSION

In conclusion, the correlation between chronic inflammation, fibrosis and cancer risk is complex, with the former being more straightforward. Chronic inflammation in the stroma of different body tissues promotes carcinogenesis *via* different mechanisms – growth factor/cytokine-mediated cellular proliferation, apoptotic resistance and immunosuppression; and free-radical-induced oxidative DNA damage. However, certain immune cells, involved in tumour-surveillance may be depleted, as seen in IPF and hepatic cirrhosis, thereby raising cancer risk by compromising immune surveillance of tumours. The relationship between stromal fibrosis and cancer risk varies in different organs, implying that the effects of fibrosis could be tissue-specific. Increased stromal fibrosis is associated with an increased cancer risk in organs like the lung, liver, biliary tract and colorectal region. Conversely, in other organs such as pancreas and potentially, oesophagus, increased stromal fibrosis may confer a lower cancer risk.

At this current time, the mechanism by which fibrosis influences cancer risk is still ambiguous. We propose two hypotheses. Firstly, a fibrotic environment contributes to an aberration in ECM dynamics which affects normal cellular behaviour and ultimately neoplastic transformation. Secondly, we hypothesise that fibrosis may present as a safe alternative to cellular regeneration which has the potential to produce aberrant DNA mutations, resulting in tumour formation. What determines the former or the latter are a multitude of factors which could include fibroblast heterogeneity and plasticity; extent of fibrosis; inflammation; and the predominance of certain mediators over others. Therefore, future studies, especially *in-vitro* and animal studies, should investigate the mechanisms by which fibrosis contributes to carcinogenesis in various organs in further depth and determine if fibrosis, alone or only in conjunction with inflammation would promote carcinogenesis. Furthermore, the role of surveillance screening and therapeutic agents with stroma manipulation potential in patients with diseases which involve chronic inflammation and fibrosis should be further studied to reduce the incidence of relevant cancers.

## FOOTNOTES

**Author contributions:** Oey O and Redfern A conceptualized the research idea; Oey O, Sunjaya AF, Khan Y, Redfern A all contributed towards study methodology, analysis, writing and editing of the manuscript; Redfern A and Yasir K supervised the manuscript preparation; All authors have read and agreed to the published version of the manuscript.



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