cost effective. Obesity has been implicated in the pathogenesis of adenocarcinoma. We aimed to assessed the role of obesity and medications on the risk of progression in BE. Methods : Patients with BE were identified from the General Practice Research Database (GPRD) which contains primary care records of over 8 million subjects. Patients with BE were identified using validated diagnostic codes. BE subjects who developed esophageal cancer (EC) more than 12 months after their first BE diagnosis were defined as progressors. Risk factors assessed included age, gender, smoking, alcohol consumption, BMI (normal < 25, overweight 25-29.9, Obese I 30-34.9, Obese II > 35) and medications (PPIs, NSAIDs, Metformin, Insulin, Statins). Time to event analysis was used to assess the overall risk of progression to EC. Cox Proportional Hazards models were used to assess predictors of progression. For medications, analyses were also conducted using time varying marginal structural models calculating the percent time subjects were on medications as per claims data. Results : 12,373 subjects with BE were identified in the GPRD database between 1996 to 2011. The mean (SD) age of these subjects was 63.04 (13.79) years. 7,905 (63.89%) were males. Of these 159 (1.3%) and 138 (1.1%) subjects developed EC more than 6 and 12 months after the first diagnosis of BE in the GPRD database. The mean (SD) follow up of subjects with BE was 4.9 (3.5) years. The incidence of EC in subjects with BE was 2.278/1000 person years of follow up. Univariate and multivariable predictors of progression to EC are presented in table 1. Increasing age, male gender and being overweight (BMI 25-29.9) were independent risk factors predictive of progression to EC. Obesity class 1 (BMI 30-34.9) showed a trend towards significance as a risk factor for progression. Among medications, NSAIDs (on time varying marginal structural analysis, OR= 0.13, 95% CI 0.05, 0.29) and Statins (on conventional analysis, OR= 0.40 , 95% CI 0.22, 0.74) were protective against EC development in BE. Metformin intake was protective (trend) in univariate analysis only. Insulin and oral anti-diabetic medications did not influence progression to EC in BE subjects. Conclusions : In this large population based cohort of subjects with BE in the United Kingdom, increasing age, male gender and higher BMI were independent risk factors for progression to EC. NSAIDs and Statins appeared to reduce the risk of progression. These factors may aid in developing a risk stratification score to predict the risk of progression and develop chemopreventive strategies in BE subjects

Table 1: Predictors of progression to Esophageal Carcinoma in BE subjects

Outcome: Esophageal Cancer				N = 9,667
Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CL)	P Value	OR (95% CL)	P Value
age	1.01 (1.00, 1.02)	0.025	1.03 (1.01, 1.04)	<0.000
male	2.48 (1.62, 3.81)	<0.000	2.69 (1.66, 4.37)	<0.000
Ever smoker	1.04 (0.74, 1.48)	0.808	xx	xx
Ever drinker	0.74 (0.37, 1.48)	0.399	xx	xx
BMI (Normal)				
Overweight (25-29.9)	1.73 (1.09, 2.76)	0.021	1.81 (1.13, 2.92)	0.014
Obese I (30-34.9)	1.25 (0.69, 2.27)	0.457	1.70 (0.91, 3.19)	0.095
Obese II	1.24 (0.17, 9.22)	0.834	2.29 (0.30, 17.7)	0.426
Drugs:				
H2 receptor blockers or PPIs	1.02 (0.65, 1.62)	0.917	0.99 (0.58, 1.70)	0.972
NSAID	0.91 (0.65, 1.29)	0.609	0.89 (0.60, 1.33)	0.580
Statin	0.41 (0.24, 0.69)	0.001	0.40 (0.22, 0.74)	0.004
Metformin	0.38 (0.12, 1.19)	0.098	0.37 (0.07, 2.11)	0.266
Insulin	0.37 (0.05, 2.64)	0.320	0.57 (0.08, 4.03)	0.571
OAD	0.51 (0.21, 1.26)	0.145	1.67 (0.46, 6.07)	0.436

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SOX2 As a Novel Marker to Predict Neoplastic Progression in Barrett's Esophagus

Sophie H. van Olphen, Katharina Biermann, Florine Kastelein, Bettina E. Hansen, Hans Stoop, Manon C. Spaander, Leendert Looijenga, Marco J. Bruno

Objective: The value of surveillance for patients with Barrett's esophagus (BE) based on histological diagnosis of low grade dysplasia (LGD) remains debated given the lack of discriminative power to stratify BE patients at high risk for neoplastic progression of those at low risk. The use of biomarkers in addition to histological assessment improves risk stratification and has the potential to improve cost-effectiveness of BE surveillance. SOX2 plays a pivotal role in the development of esophageal and gastric epithelium and is down regulated in intestinal metaplasia and gastric cancer. The aim of this study was to investigate the value of SOX2 in BE patients to predict neoplastic progression and to combine the results with our previously reported promising p53 immunohistochemical data within the same cohort. Methods: We conducted a case-control study within a large prospective cohort of 720 BE patients, with a total follow-up time of more than 5600 years. In total 44 BE patients with neoplastic progression defined as development of high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) (cases) and 44 BE patients without neoplastic progression (controls) were selected and matched for age and gender. SOX2 protein was detected by immunohistochemistry in more than 3000 biopsies and was scored independently by two investigators blinded for long-term outcome. The results were combined with p53 immunohistochemical data. Hazard ratios (HRs) were calculated by time-dependent Cox-regression models adjusted for age, gender, BE length and esophagitis. Results: Normal BE epithelium showed homogeneous strong nuclear expression of SOX2, while expression of SOX2 was progressively lost in dysplastic epithelial cells. Loss of SOX2 expression was seen in only 9.5% of biopsy series without dysplasia, in contrast to 36.8% of biopsy series with LGD and 70% of biopsy series with HGD or EAC. Multivariate analysis showed that loss of SOX2 expression (HR 3.3; 95% CI: 1.6-6.6) and aberrant p53 expression (HR 4.5; 95% CI:2.8-8.9) were independent predictors for neoplastic progression, whereas presence of LGD was no longer predictive. Aberrant expression of SOX2 and p53 strongly increases the risk to develop HGD or EAC in the individual patient (multiplied HR of 14.9). The positive predictive value for neoplastic progression increased from 47% with histological diagnosis of LGD, to 83% with LGD and concurrent aberrant SOX2 expression, to 87% with LGD and concurrent aberrant p53 expression and to 91% with aberrant SOX2 and p53 expression. Conclusion: Loss of SOX2 and aberrant p53 expression are independent predictors for neoplastic progression in patients with BE and more powerful than the histological diagnosis of LGD. SOX2 en p53 immunohistochemistry may be useful as a discriminative test to improve risk stratification of Barrett surveillance.

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Length of Barrett's Esophagus and Cancer Risk - Implications From a Population Based Study

Heiko Pohl, Haris Arash, Christian Ell, Hendrik Manner, Andrea May, Michael Vieth, Amnon Sonnenberg, Oliver Pech

Background: The risk of esophageal adenocarcinoma increases with the length of Barrett's esophagus. Understanding the risks associated with varying lengths of the Barrett segment would help designing efficacious surveillance protocols. **Objective:** To determine (a) the annual cancer transition rates of Barrett's esophagus by length of Barrett segment and (b) the number of patients who need to undergo surveillance endoscopy for the detection of one esophageal adenocarcinoma. **Methods:** The analysis relied on three different data sources. First, we obtained data on the prevalence of long (≥3cm), short (≥1cm to <3cm), and ultra-short (<1cm) segment Barrett's esophagus among a cohort of 1,017 patients with T1 esophageal adenocarcinoma. All patients had biopsy proven Barrett's esophagus. Second, we determined the overall esophageal adenocarcinoma incidence from the 2010 Surveillance Epidemiology and End Results (SEER) database among ≥50 year old individuals. Third, we performed a systematic review to estimate the prevalence of Barrett's esophagus stratified by Barrett length among ≥50 year old patients. Cancer transition rates were calculated dividing the annual number of patients with esophageal adenocarcinoma by Barrett prevalence for each category of Barrett length. **Results:** The prevalence of long, short, and ultra-short segment Barrett's esophagus among patients with T1 esophageal adenocarcinoma was 56% (95% confidence interval: 53-59%), 24% (21-26%), and 20% (18-23%). Our systematic review determined a population based Barrett prevalence of 1% for long-segment, 8% for short-segment, and 15% for ultra-short segment Barrett's esophagus. Applying these prevalence rates, long, short, and ultra-short segment Barrett's esophagus were found to be associated with an annual cancer incidence of 3.1, 0.2, and 0.1 per 1,000 patients. To detect one cancer, 318 patients with long-segment Barrett's esophagus need to undergo surveillance endoscopy; in short and ultra-short segments, the corresponding numbers of patients needed to detect one cancer are 4,349 and 9,008, respectively. **Conclusion:** Almost half of all esophageal adenocarcinomas can be attributed to patients with short or ultra-short segment Barrett's esophagus. Very large numbers of patients with short or ultra-short segment Barrett's esophagus need to undergo endoscopic surveillance to detect one cancer. From a population perspective these results question the value of surveillance in these groups.

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IL-1B and SERPINA-3 Are Novel Markers of Aggressive Barrett's Oesophagus Phenotype Using RNA Deep Sequencing Analysis

Finbar P. MacCarthy, Shane P. Duggan, Ronan Feighery, Jacintha O, Narayanasamy Ravi, Dermot Kelleher, John V. Reynolds, Dermot O'Toole

Introduction: The identification of aggressive markers in Barrett's oesophagus (BO) would help stratify groups at risk of progressing to oesophageal adenocarcinoma (OAC) allowing tailored surveillance strategies. Stratifying progressive BO risk using genomic techniques has been disappointing to date. We have applied a novel high throughput RNA sequencing analysis characterizing the BO transcriptome across the metaplasia-dysplasia sequence to identify potential markers of progression in an unbiased fashion in patients with BO. Methods: Matched biopsy samples for histology and RNA extraction were taken from BO patients of known histological grade (samples were independently examined by two expert GI pathologists to diagnose intestinal metaplasia (SIM), LGD and HGD). RNA was extracted from matched samples and sequenced to 60bp length (paired-end).21 samples were sequenced (HGD,7; LGD, 7 and SIM, 7). Reads obtained were mapped to NCBI build37.2 using TopHat. Read count generation, normalisation and differential expression (DE) analysis was performed using the HTSeq-DESeq pipeline. Significantly DE genes (>2 fold change in expression with B-H adjusted p-value <0.1) were further assessed for network and biological relevance using Ingenuity Pathway analysis. Candidate genes were selected and validated in a larger cohort (n=64) using RT-PCR and the secretion levels of candidates further validated in a larger independent cohort of patients by ELISA. Results: A mean of 52.4x106 (range 48-66x106) reads was obtained per sample.14,003 genes had ≥10 reads mapping in all samples. DE analysis was performed in 3 groups with 2 conditions at a time using the lower grade cohort as control and the higher grade as comparator: SIM vs. LGD (demonstrated 218 DE genes, 131 up-regulated in LGD, 87 down-regulated compared to SIM), SIM vs. HGD (49 DE, 27 up, 22 down) and LGD vs. HGD (317 DE, 81 up, 216 down). Network and functional analysis of DE genes confirmed overrepresentation of processes involved in oncogenesis (e.g. cell survival, proliferation, and cellular assembly). Six network-central candidate genes (FOSB, IL-1B, SERPINA3, KLK7, GSTM5 &SCUBE2) were selected for RT-PCR validation and 2 genes (IL-1B and SERPINA-3), demonstrated progressive significant increases in expression across the dysplasia sequence to OAC. This was confirmed on protein validation, with highly significant differences in secretions of IL-1B & SERPINA-3 (in serum) between SIM, dysplasia and OAC using ELISA. Conclusion: The use of RNA-sequencing as a detailed and unbiased analysis method identifies IL-1B and SERPINA-3 as novel and interesting candidates over-expressed along the metaplasia-dysplasia-cancer sequence in BO. Prospective validation of these genes as potential markers of progressive Barrett's phenotype is in progress.