**SUPPLEMENTARY FIGURES AND TABLES**

**Supplementary figure 1 Flowchart of study population**

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***Abbreviations:* PSI: Parelsnoer Institute; N: number; PALGA: Dutch nationwide network and registry of histology and cytopathology; IBD: Inflammatory bowel disease;**

**Supplementary Figure 2A-C. Kaplan Meier estimates for a CIN1 or CIN2+ lesion as worst diagnosis for IBD cohort and matched cohort by years of follow-up attained age in total study population.**

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A: Proportion of women with CIN1 as highest grade of dysplasia during follow-up. B: Proportion of women with CIN2+ as highest grade of dysplasia during follow-up. C: Proportion of women with CIN2+ as highest grade of dysplasia by attained age. *Attained age is defined as the age at diagnosis of CIN2+ or age at end of follow-up.*

***Abbreviations: CIN = cervical intraepithelial neoplasia. CIN2+ = CIN2, CIN3 or cervical cancer; IBD = inflammatory bowel disease; OR: Odds ratio. Attained age = age at diagnosis of CIN2+ or age at end of follow-up.***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **CD****N (%)** | **UC, IBD-U/I****N (%)** | ***P* value** |
| **Total number of women** |  | **1382 (65.9)** | **716 (34.1)** |  |
| **Age at IBD diagnosis** | <25 years | 586 (42.4) | 186 (26.1) | <0.001^ |
| *N/A for 5 (0.2%)* | ≥25 years | 795 (57.6) | 526 (73.9) |  |
| **Montreal L** | L1 | 256 (21.0) |  |  |
| N/A for 164 (11.9%) | L2 | 277 (22.7) |  |  |
|  | L3 | 530 (43.5) |  |  |
|  | L4 | 6 (0.5) |  |  |
|  | L1+L4 | 28 (2.3) |  |  |
|  | L2+L4 | 30 (2.5) |  |  |
|  | L3+L4 | 91 (7.5) |  |  |
| **Montreal B** | B1 | 495 (40.4) |  |  |
| N/A for 157 (11.4%) | B2 | 191 (15.6) |  |  |
|  | B3 | 192 (15.7) |  |  |
|  | B1p | 123 (10.0) |  |  |
|  | B2p | 60 (4.8) |  |  |
|  | B3p | 164 (13.4) |  |  |
| **Montreal E** | E1 |  | 56 (8.8) |  |
| N/A for 76 (10.6%) | E2 |  | 238 (37.2) |  |
|  | E3 |  | 346 (54.1) |  |
| **Smoking status** | Never | 882 (66.2) | 584 (85.0) | <0.001^ |
| *N/A for 78 (3.7%)* | Current/<6 months | 451 (33.8) | 103 (15.0) |  |
|  |  |  |  |  |
| **Education level** |  |  |  |  |
| *N/A for 46 (2.2%)* | Low  | 911 (65.4) | 472 (66.4) | 0.777^ |
|  | High  | 461 (34.6) | 239 (33.6) |  |
| **Medication exposure** |  |  |  |  |
| *N/A for 33 (1.6%)* |  |  |  |  |
|  Immunomodulator | No | 650 (47.0) | 418 (58.4) |  |
|  | <1 year | 170 (12.3) | 67 (9.4) |  |
|  | >1 year | 562 (40.7) | 231 (32.3) | <0.001^ |
| Biological | No | 796 (57.6) | 595 (83.1) |  |
|  | <1 year | 174 (12.6) | 53 (7.4) |  |
|  | >1 year | 412 (29.8) | 68 (9.5) | <0.001^ |
| **Number of screening episodes in a 5 year period** |  |  |  |  |
| *N/A for 38 (1.8%)* | 1 | 956 (69.2) | 495 (69.1) | 0.413^ |
|  | 2 | 375 (27.2) | 191 (26.7) |  |
|  | >2 | 50 (3.6) | 30 (4.2) |  |

Supplementary Table 1 Patient demographics of women with Crohn’s disease and ulcerative colitis

***Abbreviations: IBD: inflammatory bowel disease, PSI: Parelsnoer Institute, N: number; yrs: years; IQR interquartile range, CD: Crohn’s disease, UC: ulcerative colitis, IBD-U: IBD-unclassified, IBD-I: IBD-indeterminate, N/A: not applicable, L: location, B: behavior, E: extent, 5-ASA, 5-aminosalicylic acid
\* Mann-Whitney U test ^ Chi square test \*\* independent samples T-test***

**Supplementary Table 2 Standardized detection ratios of CIN2, CIN3 and cervical cancer for IBD women by age, time period and urbanization, follow-up period 2000-2016 as compared to matched cohort**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **CIN2 a** |  |  |  |  | **CIN3 a** |  |  |  | **Cervical cancer a** |  |  |  |
|  | **No. prim. testsb** | **Obsb** | **Expb** | **SDRb** | **95% CIc** |  | **Obsb** | **Expb** | **SDRb** | **95% CIc** | **Obs b** | **Expb** | **SDRb** | **95% CIc** |
| **Overall detection rateb** | **6,654** | 52 | 34 | **1.53** | **1.14-2.01** |  | 64 | 52.7 | 1.21 | 0.94-1.55 | 2 | 6.7 | 0.30 | 0.03-1.08 |
| **Screening age** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **<29** | 348 | 7 | 8.3 | 0.84 | 0.34-1.74 |  | 5 | 8.0 | 0.63 | 0.20-1.46 | 0 | 0.3 |  |  |
| **29-34** | 1,457 | 15 | 11.7 | 1.28 | 0.71-2.12 |  | 25 | 21.7 | 1.15 | 0.75-1.70 | 0 | 1.5 |  |  |
| **35-39** | 1,068 | 11 | 4.2 | **2.62** | **1.31-4.69** |  | 11 | 7.9 | 1.39 | 0.69-2.49 | 1 | 1.1 | 0.91 | 0.01-5.06 |
| **40-44** | 1,136 | 10 | 4.3 | **2.33** | **1.11-4.28** |  | 7 | 5.7 | 1.23 | 0.49-2.53 | 0 | 0 |  |  |
| **45-49** | 1,060 | 5 | 2.4 | 2.08 | 0.67-4.86 |  | 8 | 4.2 | 1.91 | 0.82-3.75 | 1 | 1.1 | 0.91 | 0.01-5.06 |
| **50-54** | 706 | 1 | 1.5 | 0.67 | 0.02-3.72 |  | 5 | 2.1 | 1.91 | 0.51-4.88 | 0 | 0.7 |  |  |
| **55-59** | 594 | 3 | 0.9 | 3.33 | 0.67-9.74 |  | 2 | 1.2 | 1.67 | 0.20-6.02 | 0 | 0.6 |  |  |
| **≥60**  | 285 | 0 | 0 |  |  |  | 1 | 0.6 | 1.67 | 0.02-9.27 | 0 | 0.3 |  |  |
| **Total** | 6,654 | 52 | 33 | **1.57** | **1.17-2.05** |  | 64 | 51.4 | 1.25 | 0.96-1.59 | 2 | 5.5 | 0.36 | 0.04-1.31 |
| **Time period** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **2000-2005** | 2,157 | 12 | 7.9 | 1.52 | 0.78-2.65 |  | 19 | 17.3 | 1.10 | 0.66-1.72 | 0 | 2.2 |  |  |
| **2006-2010** | 2,006 | 19 | 8.7 | **2.18** | **1.31-3.41** |  | 19 | 16.0 | 1.19 | 0.71-1.85 | 0 | 2.0 |  |  |
| **2011-2016** | 2,491 | 21 | 17.7 | 1.19 | 0.73-1.81 |  | 26 | 17.4 | 1.49 | 0.98-2.19 | 2 | 2.5 | 0.80 | 0.10-2.89 |
| **Total** | 6,654 | 52 | 34.3 | **1.51** | **1.13-1.98** |  | 64 | 50.7 | 1.26 | 0.97-1.61 | 2 | 6.6 | 0.30 | 0.03-1.10 |
| **Urbanization** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **High level** | 1,962 | 17 | 15.4 | 1.10 | 0.64-1.77 |  | 24 | 17.2 | 1.40 | 0.89-2.08 | 2 | 0.6 |  |  |
| **Low level** | 4,692 | 35 | 23.0 | **1.52** | **1.06-2.12** |  | 40 | 31.7 | 1.26 | 0.90-1.72 | 0 | 4.7 |  |  |
| **Total** | 6,654 | 52 | 38.4 | **1.35** | **1.01-1.78** |  | 64 | 48.9 | **1.31** | **1.01-1.67** | 2 | 5.3 | 0.38 | 0.04-1.37 |

***a CIN: Cervical intraepithelial neoplasia; CIN1: mild dysplasia; CIN2: moderate dysplasia; CIN3: severe dysplasia or carcinoma in situ; cervical cancer: invasive cervical squamous cell carcinoma and non-clear cell adenocarcinoma; CIN2+: CIN2 or worse
b No. of prim tests: number of primary screening tests; Detection rate is the percentage of episodes starting with a primary cytology or histology screen test resulting in a histological diagnosis of CIN or cervical cancer.* Obs: detection rate in the IBD cohort. Exp: detection rate in the age and year of screening matched cohort. *SDR Standardized detection ratio: defined as observed detection rate in IBD cohort compared to the expected detection rate.
c 95% CI: 95% confidence interval based on a Poisson distribution. Bold numbers: statistically different.***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

***S*upplementary Table 3 Observed number of CIN and cervical cancer cases, person-years, incidence rates per 1,000 person-years and incidence rate ratios for women with IBD compared to matched women from general population in total study population**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Person-years** | **Obs-No** | **IR (95% CI)** | **IRR (95% CI)** |
| CIN1 |  |  |  |  |
|  IBD women | 24,737 | 31 | 1.25 (0.85-1.80) | 1.09 (0.73-1.61) |
|  Matched women | 98,730 | 114 | 1.16 (0.95-1.39) |  |
| CIN2 |  |  |  |  |
|  IBD women | 24,624 | 46 | 1.87 (1.37-2.49) | **1.58 (1.12-2.22)** |
|  Matched women | 98,821 | 117 | 1.18 (0.98-1.42) |  |
| CIN3 |  |  |  |  |
|  IBD women | 24,482 | 61 | 2.49 (1.91-3.20) | **1.34 (1.00-1.78)** |
|  Matched women | 98,083 | 183 | 1.86 (1.60-2.16) |  |
| Cervical cancer |  |  |  |  |
|  IBD women | 24,936 | 2 | 0.08 (0.01-0.27) | 0.40 (0.06-1.47) |
|  Matched women | 99,406 | 20 | 0.20 (0.13-0.31) |  |
| CIN2+ |  |  |  |  |
|  IBD women | 24,159 | 109 | 4.51 (3.71-5.44) | **1.37 (1.10-1.70)** |
|  Matched women | 97,163 | 320 | 3.29 (2.94-3.68) |  |

*Abbreviations: CI: confidence interval; CIN, cervical intraepithelial neoplasia; CIN2+, CIN2, 3 or cervical cancer; IBD: inflammatory bowel disease. No. number; IR incidence rate; IRR incidence rate ratio*

|  |  |
| --- | --- |
|  | **CIN2+** |
|  | **Univariable** | **Multivariable** |
|  | **HR** | **95%CI** | **HR** | **95%CI** |
| **Case** |  |  |  |  |
|  **No IBD** | 1.00 | Reference | 1.00 | Reference |
|  IBD | 1.37 | 1.10-1.70 | 1.28 | 1.03-1.60 |
| **Urbanization** |  |  |  |  |
|  Low level | 1.00 | Reference | 1.00 | Reference |
|  High level | 1.31 | 1.07-1.60 | 1.33 | 1.09-1.62 |
| **Screening episodes in a 5 year period** |  |  |  |  |
|  1 episode | 1.00 | Reference | 1.00 | Reference |
|  1-2 episodes | 1.31 | 1.05-1.63 | 1.28 | 1.03-1.60 |
|  >2 episodes | 3.42 | 2.31-5.07 | 3.31 | 2.22-4.92 |

Supplementary Table 4 Univariable and multivariable Hazard ratios for different risk factors for CIN2+ over time in total study population

***Abbreviations: CIN: Cervical intraepithelial neoplasia. CIN2+: CIN2, CIN 3 or cervical cancer; IBD: inflammatory bowel disease. HR: Hazard ratio, CI: confidence interval***