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Supplementary information

Is early-onset cancer an emerging global epidemic? Current evidence and future implications

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Supplementary Table 1. Trends in incidence of selected early-onset cancer types

Country	Breast cancer			Colorectal cancer						Endometrial cancer			Oesophageal cancer						Extrahepatic bile duct cancer and gallbladder cancer					
	Female			Female			Male			Female			Female			Male			Female			Male		
	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI
Australia	0.5	0.2	0.8	1.8	0.9	2.6	2.7	1.7	3.7	1.7	0.2	3.2	-0.8	-5	3.6	0	-1.9	1.9	2.4	-0.7	5.5	-1.8	-5.4	1.9
Belarus	0.8	0	1.5	-0.1	-1.3	1.1	1.7	0.2	3.2	3.4	1.8	4.9	3.7	-6.8	15.3	0.7	-1.4	2.8	9.8	1.1	19.2	1.3	-3.4	6.2
Brazil	-1.7	-3.4	0	0.7	-4.1	5.6	-0.2	-4.1	3.7	-2.2	-10.1	6.4	4.9	-10.6	23.2	-7.3	-12.1	-2.3	-7.2	-18	4.9	5.1	-3.6	14.5
Bulgaria	0.4	0.2	0.7	0.1	-1.6	1.8	-0.9	-2.4	0.5	2.2	0.5	4	5.3	-4.9	16.6	0.9	-2.1	3.9	-1.6	-8.9	6.4	4.1	0.2	8.1
Canada	0.6	0.2	1	2.1	1.3	2.9	1.8	1	2.6	3.6	2.3	4.9	1.8	-4.5	8.5	1.8	-0.2	3.9	3.8	0	7.7	3.6	0.9	6.4
Chile	-0.9	-4.7	3	-0.6	-9.5	9.2	-0.2	-7.3	7.5	-1	-14.6	14.7	1	-10.7	14.2	-0.6	-8.9	8.4	-2.9	-9	3.5	1.4	-6.9	10.4
China	1.6	1.1	2.1	-0.8	-2.1	0.5	1.3	0.1	2.6	2.7	1.5	4	-1.2	-18.3	19.3	-5.2	-7.1	-3.3	-4	-6.8	-1.2	0.7	-2.8	4.3
Colombia	-1.2	-2.2	-0.3	4.5	-5.6	15.7	4.5	-6.6	16.9	-2.1	-6.9	3	-6	-16.7	6.1	-8.6	-18.3	2.2	-3.3	-10.3	4.3	2.7	-7.1	13.5
Costa Rica	0.6	-1	2.2	1.4	-2	4.9	2.6	0.3	4.9	1.6	-4.9	8.6	3.6	-10.5	19.9	-	-	-	-6	-13.1	1.7	-13.4	-24	-1.2
Croatia	1.5	0.1	2.9	-0.9	-2.9	1.1	-2.4	-4.3	-0.4	5.1	2.2	8.2	-8.9	-16.9	-0.1	-5.1	-8.2	-1.8	-7.6	-18.2	4.2	-0.2	-10.3	11.2
Czech	1.9	1.1	2.6	0	-0.7	0.7	-2.3	-3.5	-1.1	0.3	-1	1.6	-8.9	-16.9	-0.1	-2.2	-5.8	1.5	-9.5	-14.7	-4	-8.5	-13.1	-3.7
Denmark	0.5	-0.2	1.2	2.2	0.9	3.5	0.5	-0.5	1.5	1.6	-1.8	5	-0.7	-7.9	7.1	-4.3	-10.4	2.2	4.8	-4.3	14.8	-2.4	-10.4	6.3
Ecuador	0.9	-0.8	2.5	4.8	0.8	8.9	3	-3.2	9.7	6.7	-2	16.2	3.6	-6.4	14.5	-4	-14.2	7.4	-4.6	-11.5	2.8	-6.5	-14.7	2.5
Estonia	1.3	-0.2	2.8	0.2	-4.4	5	1.6	-2.9	6.3	3.6	-0.8	8.2	1.2	-13	17.8	-1.9	-10.4	7.5	4.7	-8.1	19.4	4.8	-4.1	14.5
France	0.8	0	1.6	1.8	0.4	3.3	-0.9	-2.9	1.1	-4.6	-7.6	-1.4	1.5	0.2	2.8	-5.9	-7.4	-4.4	1.8	-3.8	7.6	1.1	-9.2	12.5
Germany	1.7	0.7	2.6	1.5	-0.4	3.5	2	0	4.1	4.5	1.1	8	3.5	-7	15.2	0	-4	4.1	5.7	-0.8	12.6	4.9	-3	13.4
Iceland	1.1	-0.7	2.9	1.3	-8.1	11.5	4.4	-4	13.5	2.1	-8.2	13.5	0.1	-8.6	9.6	2.3	-7.2	12.7	-	-	-	-1.1	-39.1	60.6
India	-0.4	-2.3	1.5	1	-2.1	4.2	2.9	-0.1	6	3.4	-3.4	10.7	-4.6	-8.4	-0.6	-7.6	-13.3	-1.4	6.6	0	13.7	4.3	-2.7	11.8
Ireland	1.4	0.6	2.2	0.6	-1.5	2.7	1.3	-1	3.7	1.2	-1.3	3.8	-4.4	-10.5	2.2	-2.6	-7	2	-3.7	-12.1	5.6	0.5	-8.1	9.9
Israel	-0.6	-1.3	0.1	-1.1	-2.6	0.5	0	-1	0.9	-2.2	-3.8	-0.5	-1.8	-13.4	11.3	-4.5	-10.3	1.7	-3	-10.5	5.2	-9.3	-16.3	-1.6
Italy	0.6	-1	2.3	-1	-3.7	1.7	-0.6	-2.6	1.5	1	-1.9	3.9	1.6	-7.7	11.8	3	-3.8	10.2	3.9	-4.1	12.6	2.8	-6	12.3
Japan	3.4	2.5	4.3	1.8	0.5	3.1	-0.9	-2.3	0.4	9.4	4.9	14.2	6.8	-0.8	14.9	-3.8	-7.3	-0.1	-5.1	-7.7	-2.3	-2.7	-7.2	2
Kuwait	0.9	-1.4	3.3	-0.4	-7.1	6.7	6.3	0	13.1	-	-	-	-8.6	-	-	-1	-11	10.1	-7.5	-15.8	1.7	-	-	-
Latvia	0.8	-0.2	1.9	2.2	-1.2	5.9	1.3	-1.3	3.9	0.3	-3.2	4	-1.8	-8	4.9	-2.3	-7.8	3.4	0.7	-7.3	9.5	-10.8	-20.9	0.5
Lithuania	0.4	-0.6	1.4	0.7	-2.1	3.5	-2.3	-4.1	-0.4	0.9	-2.1	3.9	12.8	6.5	19.5	0.9	-2.2	4.1	-3.8	-11.6	4.7	-2.8	-13.1	8.7
Malta	2.7	0.8	4.6	-2.3	-11.6	8	0.9	-6.3	8.7	-10.5	-18.7	-1.3	-	-	-	6.4	-3.2	17	-	-	-	-	-	-
New Zealand	1.4	0.7	2.1	0.6	-1	2.3	2.5	0.9	4	5.6	3.8	7.5	8	-4.4	22.1	-0.7	-6.9	6	3.6	-6.9	15.3	2.3	-7.5	13.2
Norway	0.9	0	1.8	1	-0.9	2.9	0.7	-1.1	2.5	-0.8	-3.5	2	-1.3	-9.3	7.4	4	-0.8	9.1	-0.6	-6.3	5.3	-1.5	-10.1	8
Poland	0.5	-1.7	2.8	-0.4	-3.2	2.5	1	-2.4	4.5	0.1	-4.5	4.9	-	-	-	-7	-16.5	3.7	0.4	-9.9	12	1.1	-4.5	7.2
Republic of Korea	4.4	3.8	5	4.6	3.9	5.3	5.1	4.4	5.8	5.2	4	6.5	5.1	-6.8	18.5	-2.2	-5	0.6	-3.1	-5.1	-0.9	-0.5	-2.5	1.4
Slovakia	1.9	1.3	2.5	1.4	-0.5	3.3	1.5	-0.1	3.3	0.9	-1	2.8	-4.7	-15.6	7.7	-6.9	-10.8	-2.8	-8.1	-15.3	-0.2	-8.9	-25	10.7
Slovenia	0.6	-0.7	1.8	2.1	-1	5.3	0.2	-1.5	1.9	-0.7	-3.4	2.1	-1.4	-12.8	11.5	-5.9	-13.1	1.8	-0.9	-11.7	11.3	-4.1	-12.2	4.7
Spain	0.5	-0.1	1.2	-0.9	-2.7	0.9	-0.5	-2.2	1.2	-1.2	-4.3	2.1	2.1	-3.8	8.3	-7.3	-10.3	-4.2	-2.2	-7.5	3.4	-0.7	-11.7	11.8

Sweden	0.8	0.1	1.5	1.1	-0.5	2.7	2.6	1	4.2	2.1	-0.8	5.1	-1.2	-9.6	8	-0.6	-4.7	3.7	2.4	-2.6	7.8	6.9	1.6	12.5
Switzerland	0.5	-0.4	1.5	2.4	-1.1	6	0.3	-2.5	3.2	1.2	-2.1	4.7	-3.7	-15.1	9.2	-6.8	-13.4	0.3	0.8	-8.9	11.5	-2.3	-11	7.2
Thailand	1.1	0.2	2.1	0.3	-1.8	2.4	3.6	2.5	4.8	3.4	-1.1	8	-2.7	-13.2	9	8.8	4.9	12.8	3.2	-2.6	9.4	4	-0.8	9
The Netherlands	0.8	0.3	1.3	1.9	1.2	2.6	2.1	1.5	2.7	-0.6	-2.2	1	-2.4	-5.3	0.6	-0.4	-2.4	1.6	-0.4	-3.9	3.2	0.1	-3.2	3.6
Turkey	2.2	1.4	3	2.8	0.7	4.9	0.9	-0.6	2.5	2.9	0.7	5.2	3.6	-3.3	11.1	-5.3	-10.2	-0.1	-0.8	-5.5	4.1	6.4	-3.7	17.5
UK, England & Wales	1.1	0.4	1.8	2.8	1.8	3.7	2.5	1.9	3.2	3.1	1.9	4.4	-1	-3	1.1	-1.3	-9.6	7.7	2.4	0.2	4.5	3.4	0	6.9
UK, Northern Ireland	0.3	-0.7	1.4	1.4	-1.7	4.6	4.3	-0.3	9.1	2.8	-0.1	5.7	1.1	-7.4	10.3	-0.3	-1.8	1.3	7.5	-0.5	16.2	3.8	-8.3	17.6
UK, Scotland	1	0.5	1.5	3.2	1.6	4.8	0.2	-1.7	2.1	-0.2	-3.5	3.4	-1.5	-7.2	4.6	0.1	-2	2.3	6.2	-4.6	18.2	-3	-9.6	4
Ukraine	-0.2	-0.8	0.4	0	-1	1	0.1	-0.7	0.9	0.9	0.1	1.7	6.3	1.2	11.7	0.8	-2.2	3.9	-1.4	-4.7	2	3.3	-0.7	7.5
USA	0.2	0	0.5	1.9	1.4	2.5	1.6	1.2	2	2.1	1.6	2.5	-4.1	-7.1	-1	-1.6	-3	-0.2	1	-1.7	3.8	0.9	-1.1	3
Uganda	2.1	-1.8	6.2	5.6	-4	16.2	-1.2	-7.6	5.6	-2.8	-15.6	12	12	5	19.6	5	1	9.1	4.5	-41.6	87.1	-	-	-

Country	Head and neck						Kidney						Liver						Myeloma					
	Female			Male			Female			Male			Female			Male			Female			Male		
	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI
Australia	1.1	-1	3.3	-0.9	-2	0.1	2.1	0.4	3.9	3.8	2	5.5	4.2	0.8	7.7	2.3	0.3	4.2	3	-0.6	6.7	1.9	-0.2	4.1
Belarus	6	2.1	10.1	0.5	-0.5	1.4	2	0.8	3.1	3.5	2.1	4.8	0.9	-3.2	5.2	2.3	-11.6	18.4	3	0	6	2	-2.1	6.4
Brazil	2	-4.5	9	-2.2	-5	0.6	13.4	4.8	22.8	-0.1	-9.3	10	-3.3	-12.2	6.6	1.4	-9.9	14.2	-2.7	-17	14	4.3	-8.2	18.5
Bulgaria	4.5	1.8	7.3	-1.4	-3	0.2	3.1	-1.2	7.5	2.9	-0.1	6	4.5	-4.6	14.5	-0.4	-5.4	4.9	3.1	-7.3	14.7	2.3	-8.4	14.1
Canada	0.4	-0.9	1.7	-0.6	-1.5	0.4	1.6	-0.3	3.7	2.8	1.7	4	5	2.2	7.9	-2	-3.6	-0.4	1.5	-0.7	3.9	0.8	-0.8	2.3
Chile	-1.3	-22.4	25.4	2.5	-7.9	14	3	-7.1	14.1	-7.5	-12	-2.8	-9.8	-27.7	12.6	5.9	-7.7	21.6	-0.9	-24	29.1	-3.2	-11.5	5.9
China	-1.6	-2.6	-0.6	-1.4	-2.3	-0.5	3.1	0.4	5.9	7.5	5.7	9.3	-3.3	-4.8	-1.8	-5.7	-7.8	-3.5	1.3	-7.2	10.6	-1.9	-4.4	0.6
Colombia	2.6	-0.1	5.3	-0.2	-5.4	5.2	-2.6	-15.3	11.9	-1.5	-11.6	9.7	2.7	-6.4	12.7	-8.5	-19.9	4.6	1.6	-8.4	12.7	-2.1	-11.3	8.1
Costa Rica	-1.3	-8.2	6	-4.7	-8.6	-0.6	-2.6	-8.7	4	0.1	-5.6	6.2	1.6	-5.1	8.8	-6.7	-12.2	-0.7	-1.2	-15.5	15.6	-2.3	-11.9	8.3
Croatia	-0.1	-4.1	4.1	-5.9	-7.9	-3.9	0.2	-3.3	3.7	-0.4	-2.4	1.7	-5.4	-10	-0.6	-2.2	-7	2.8	-2	-6.8	3	-6.5	-10.8	-2
Czech	1.7	-0.6	4.1	-3.5	-4.7	-2.2	-1.6	-3.8	0.5	-0.5	-1.8	0.8	-1.7	-8.7	5.7	-5.7	-8.7	-2.5	0.5	-4.3	5.5	-0.4	-6.6	6.2
Denmark	-1.3	-3.9	1.4	-2	-3.9	-0.1	7.1	1	13.6	6	3.8	8.1	-0.6	-8.4	7.9	-3.7	-10.1	3.1	4.7	0.8	8.9	0.1	-3.9	4.3
Ecuador	4.6	-4.2	14.3	25.5	18.3	33.1	4.4	-4.9	14.5	12.1	-21.9	60.7	1.8	-7.2	11.7	2.7	-3	8.8	-1.1	-6.7	4.9	3.5	-4.6	12.2
Estonia	4.3	-4.5	14	-3.6	-8.7	1.7	0.7	-6.1	7.9	-0.2	-4.6	4.5	-3.1	-12.5	7.5	3.3	-4.4	11.6	-4.5	-16.5	9.1	4.1	-1.3	9.8
France	0.7	-2.5	4	-7.7	-9	-6.4	4.9	2	8	2.7	0.2	5.2	-1.6	-7.3	4.4	3.1	-0.1	6.5	2.5	-3.3	8.7	1.5	-1.8	4.9
Germany	-6.3	-10.2	-2.2	-6.9	-9.4	-4.4	3.3	-0.2	7	-1.2	-4.3	2	3.5	-3.4	11	4.2	-2.3	11.2	-0.1	-8.3	8.7	2.1	-5	9.8
Iceland	-6.5	-16	4.2	2.6	-6.5	12.6	4	-14.3	26	0.6	-5.4	6.9	-2.8	-12.7	8.3	5.9	-28.5	56.8	-2.7	-15.3	11.8	-0.4	-1.8	1.1
India	1	-1.7	3.8	3.9	2.6	5.2	3.9	-8.6	18	-0.8	-8	7	1.1	-10.6	14.4	1.5	-4.2	7.6	-0.1	-7.7	8.1	6.4	2.5	10.5
Ireland	7.9	3.3	12.7	1.8	-1.4	5.1	4.6	1.8	7.4	4.9	1.8	8	4	-6.7	15.9	9.3	4.8	14	0.6	-6.3	8.1	-0.4	-8.1	7.9
Israel	0	-3.5	3.5	-3.5	-6.5	-0.3	0.7	-1.9	3.4	0.7	-2.2	3.7	-0.5	-5.7	5	-0.1	-7.9	8.5	-5.8	-12	0.9	-0.5	-3.1	2.2
Italy	-0.4	-6.6	6.1	0	-2.3	2.2	2.4	-2	7	4.4	1.5	7.3	5.9	-5.5	18.6	2.7	-0.5	6	-4.2	-12	4.3	-0.8	-5.6	4.3
Japan	4.9	0.9	9.2	1.7	-1.3	4.8	6.3	2.1	10.7	6.5	4.1	8.9	-2.2	-8.4	4.4	-6.6	-8.1	-5.1	2.6	-2.5	7.9	-1.7	-11.8	9.4
Kuwait	-2.2	-12.9	9.8	1.3	-6.2	9.5	2.2	-14.8	22.8	7.3	-2.7	18.4	-6.4	-13.1	0.8	-2.9	-22.1	21	-5.3	-10.9	0.6	5.5	-18.4	36.5
Latvia	2.5	-7	13	2.9	-1.5	7.5	2.9	-2.8	8.9	2.4	-0.7	5.6	-6.3	-16.5	5.2	2.2	-3.2	7.8	8.6	-0.5	18.6	7.6	-31.2	68.2

Lithuania	1.1	-4.1	6.6	-0.3	-3.3	2.8	3	0.2	5.8	2.8	0.9	4.7	-1.4	-12.7	11.3	7.9	1.5	14.8	5.9	-1.1	13.4	10.2	2.6	18.3
Malta	5.8	-1.5	13.6	3.2	-4.3	11.4	12.3	-0.9	27.3	4.1	-4.6	13.5	-	-	-	6.5	-14.4	32.5	1.7	-0.4	3.8	6	-4.3	17.5
New Zealand	0.1	-2.5	2.8	1.4	-0.1	2.9	0.7	-2.6	4.2	4.5	2	7	-1.2	-6.5	4.4	0.3	-3.9	4.7	2.4	-3	8.1	2.6	-1.3	6.6
Norway	4.5	0.8	8.3	-2.3	-5.1	0.7	6.6	0.9	12.7	3.3	-0.7	7.6	4.7	-8.1	19.3	6	0.8	11.5	1.6	-4.4	7.9	0.9	-4.8	7
Poland	0.6	-8.1	10	0.2	-5.6	6.4	-1.5	-5.1	2.3	-1.3	-5.8	3.4	-0.3	-10.6	11.2	5.2	-5.3	16.7	-7.9	-14.4	-0.9	-3.8	-11.8	4.9
Republic of Korea	3	1.7	4.3	2.6	1.1	4.1	6.5	4.3	8.9	6.6	5.3	7.9	-2.5	-3.6	-1.3	-4.5	-6.5	-2.4	5.1	1.4	8.9	1.3	-1.2	3.9
Slovakia	1.2	-3.6	6.2	-6.3	-7.5	-5.1	4.2	1.1	7.5	5.3	3	7.6	3.4	-2.9	10.1	0.3	-4.9	5.8	0.9	-3.8	5.9	4.8	-2.2	12.3
Slovenia	-0.6	-5.1	4.1	-3.4	-5.8	-1	-0.2	-4.4	4.1	3.9	0.1	7.9	-2.4	-10.9	6.8	-7.2	-14.3	0.5	8.8	-2.5	21.3	-3.3	-16.9	12.4
Spain	-3.4	-6.7	-0.1	-6.8	-8.5	-5.1	0.5	-2.3	3.3	-0.5	-2.8	1.8	0.4	-6.5	7.9	5.5	2	9.1	3.7	-2.3	10	-0.7	-5.5	4.4
Sweden	0.6	-1.5	2.7	-0.4	-2.1	1.3	2.5	-0.9	5.9	3.8	1.3	6.3	3.5	-9.8	18.9	2.5	-0.6	5.6	2.1	-2.3	6.6	-0.9	-7.9	6.7
Switzerland	0.6	-3.7	5.1	-5.4	-8.1	-2.6	1.8	-3.3	7.2	1.4	-0.8	3.6	2.3	-6.5	11.8	-3.8	-7	-0.5	7.8	-0.6	16.8	-0.4	-9.3	9.4
Thailand	-0.8	-2.4	0.8	0.9	-1.1	3	2.8	-7.2	14	6	-2	14.5	-3.6	-6.1	-1.1	-0.8	-2.4	0.9	0.3	-7.3	8.6	5.6	-2.8	14.8
The Netherlands	-0.4	-2.3	1.5	-1.9	-4	0.2	3.9	1.5	6.4	3.8	2.6	5.1	4.7	-0.7	10.3	2.2	-0.5	5	0.4	-2.8	3.8	0.3	-1.7	2.3
Turkey	0.8	-2.5	4.1	1.1	-1.1	3.3	4.8	2.3	7.4	5.8	2.9	8.8	-3.4	-8.2	1.6	-1.8	-6	2.5	6.7	-1.3	15.4	2.1	-1	5.3
UK, England & Wales	2.8	1.5	4.1	2.4	2.1	2.7	4	2.9	5.1	4.1	3.2	5	4.8	2.8	7	2	-0.5	4.5	4.7	2.5	6.9	2.8	0.9	4.7
UK, Northern Ireland	9.1	3.8	14.7	3.5	-1.2	8.5	2.8	-4.2	10.3	6.1	2.2	10.1	0.2	-8.7	10	4.9	-5.3	16.3	0.6	-9.3	11.7	-3.5	-13.3	7.4
UK, Scotland	4.7	0	9.5	0.1	-4.4	4.8	6.1	2.3	10.1	3.2	1.3	5.2	3.2	-3.4	10.1	5.8	1	10.9	2.4	-4.4	9.7	2.8	-2.5	8.5
Ukraine	1	-0.7	2.7	-0.1	-1.8	1.6	1.6	0	3.3	1.3	0.3	2.3	-1.3	-6.8	4.5	-1.6	-4.6	1.5	-1.3	-4.9	2.5	0.8	-2.7	4.5
USA	-0.4	-1.5	0.6	-0.9	-2	0.1	3.6	2.3	4.9	4.1	3.4	4.9	0.4	-2	2.7	-1.6	-5.6	2.4	2	-0.6	4.7	3	1.3	4.8
Uganda	-2.5	-9.8	5.5	-0.3	-8.1	8.2	1.6	-10.4	15.1	-2.1	-19.3	18.9	9.5	2	17.6	6.6	0.9	12.7	6.8	-11.8	29.3	0.7	-13.2	16.9

Country	Pancreatic cancer						Prostate cancer			Stomach cancer						Thyroid cancer					
	Female			Male			Male			Female			Male			Female			Male		
	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI	AAPC	LCI	UCI
Australia	1.7	0.4	3	1.6	-0.2	3.4	12	7	17.3	-1.1	-3.2	1.1	-1.2	-3	0.6	4.1	3.6	4.6	4.9	3.2	6.6
Belarus	0.2	-3.1	3.6	2.5	0.9	4.2	7	3.2	10.8	-1.7	-3.8	0.5	-2.8	-3.3	-2.2	1.6	0.7	2.5	0	-1.7	1.8
Brazil	1.6	-8.4	12.7	2.9	-5.7	12.4	9	3.8	14.4	-1.9	-6.3	2.8	-2.1	-8.1	4.3	4.1	0.5	7.7	6.6	0.8	12.9
Bulgaria	0.9	-3.4	5.4	-1	-3.4	1.4	-2.7	-9.5	4.6	-0.8	-2.2	0.5	-2.8	-5.2	-0.4	5	2.7	7.4	4.4	0.5	8.5
Canada	2.2	0.4	4	2.6	0.8	4.4	2	-0.7	4.7	1.9	0.2	3.6	0.1	-2	2.2	4.6	3.8	5.4	6.3	5	7.7
Chile	-1.8	-12.8	10.7	-3	-15.5	11.3	-1.9	-10.5	7.5	-6.6	-13.3	0.6	-12.2	-22.8	-0.1	7.4	0.8	14.4	0.7	-7.7	9.8
China	-3.5	-8.4	1.6	-0.6	-3.8	2.7	18.1	12.2	24.2	-3.1	-4.6	-1.6	-5.5	-6.4	-4.7	12.7	11.4	14.1	16.9	13.7	20.3
Colombia	-6	-13.9	2.7	8	-4.4	21.9	5.3	-5.1	16.8	1	-2.9	5.2	-1.4	-5.1	2.4	3.1	0.2	6.2	4.3	-1.3	10.2
Costa Rica	-4.1	-9.6	1.8	-2.9	-6	0.4	7.3	0.9	14.1	0.8	-2.2	4	-3.5	-5	-2	8.4	7	9.8	9.1	3.8	14.8
Croatia	0.3	-5	5.8	-3.4	-7.5	1	2.5	-4	9.4	-4.9	-8.6	-1.1	-3.9	-6.1	-1.6	4.6	1.2	8.1	5.3	2.3	8.3
Czech	1.9	-0.9	4.8	-1.2	-3	0.6	13.3	9.5	17.1	-1.6	-4	0.8	-2.2	-4.4	-0.1	7.2	5.4	9.1	6.8	4.8	8.8
Denmark	0.1	-3.8	4.1	-0.7	-4.5	3.1	15.2	9.3	21.5	0.1	-5.1	5.6	-1.8	-6.1	2.7	5.3	4.1	6.6	6.3	2.5	10.1
Ecuador	-6.5	-20.2	9.4	-3	-11.6	6.4	10.5	3.1	18.3	3.9	1.2	6.7	0.5	-2.6	3.7	14.6	12.6	16.7	14.8	5.7	24.6
Estonia	-3.5	-10.8	4.3	-4	-8.3	0.6	22.6	13.1	32.9	-4.3	-9.5	1.2	-2.8	-5.7	0.2	0.8	-4.1	6	4.4	-6.3	16.4
France	1.2	-2.7	5.2	4	0.9	7.3	5.9	1.7	10.2	-3.4	-7.3	0.7	-0.3	-3.2	2.6	4.3	3.3	5.2	3	0.5	5.6

Germany	1.6	-4.3	7.9	-2.3	-18.1	16.6	1.9	-1.7	5.5	-2.2	-7.7	3.7	-2.5	-4.8	-0.1	5.9	0.8	11.3	2.8	-1.4	7.2
Iceland	-0.3	-13.2	14.5	0.5	-13.9	17.2	10.6	1.7	20.2	-1.2	-9.5	7.8	4.9	-7.3	18.7	1.7	-4.7	8.5	-0.5	-13.7	14.8
India	0.2	-7.8	9	5.7	-1.7	13.7	3.2	-9.3	17.3	0.6	-2.5	3.9	-0.9	-3.8	2.1	0.2	-3.7	4.2	1.1	-7.6	10.7
Ireland	-1.1	-6.8	4.8	-1.4	-7.7	5.4	12.1	9.1	15.3	-0.2	-3.7	3.4	-1.2	-3.6	1.2	10.1	7.6	12.7	8.2	3.7	12.9
Israel	-3.1	-6.9	0.8	-2.6	-6.5	1.4	0.7	-5.8	7.7	-1.4	-4.8	2.1	-1.4	-4.2	1.4	3.4	2.4	4.3	4.7	1.4	8.1
Italy	0.6	-5	6.5	2.1	-3.5	8	11.4	5.8	17.4	-4.6	-8.3	-0.8	-4.5	-8.8	0.1	3.3	-2.2	9.2	6.2	3	9.5
Japan	2.8	-2.8	8.7	-0.5	-5.6	4.9	22	8.6	36.9	-3.5	-5.7	-1.2	-5	-6.7	-3.3	6.5	3.8	9.3	6.9	2.4	11.5
Kuwait	0.7	-7.1	9.2	-8	-20.2	6	2.9	-27.7	46.7	4.2	-4.9	14.3	-9.7	-23.3	6.3	4.9	1	8.8	-1.4	-5.9	3.4
Latvia	-8	-15.3	-0.1	-1	-6.1	4.4	6.1	-1	13.8	0.3	-4.5	5.3	-4.6	-7.2	-2	13.1	9.6	16.6	10.8	5.9	16
Lithuania	-0.1	-4.2	4.2	-3.6	-6.1	-1.1	12.4	-1.6	28.3	-0.7	-4.3	3	-1.3	-3.6	1	2.7	0	5.6	7.6	3.4	12
Malta	-4.4	-11.7	3.5	-2.7	-12	7.7	-4.8	-13.8	5.2	-0.3	-10.6	11.2	4.7	-6.2	16.8	6.1	-1.9	14.9	12.1	-0.1	25.8
New Zealand	4.8	-1.6	11.7	3.1	-3.1	9.7	3.7	0.1	7.4	1	-2.9	5	1.8	-1.6	5.3	4	1.5	6.4	4.4	0.6	8.3
Norway	-0.2	-5.1	4.9	0.8	-3.1	4.8	9	6.3	11.9	-5.5	-9.3	-1.5	3.3	0.3	6.4	3.7	1.7	5.8	4.2	0.5	7.9
Poland	-2.1	-12.5	9.5	-4.7	-10.2	1.1	2.4	-6.7	12.4	5.2	-6.4	18.2	2.8	-2.7	8.6	3.3	-0.4	7.2	6.9	-2.4	17.2
Republic of Korea	1.9	-0.6	4.4	0.6	-1.6	2.7	16.3	10.1	22.8	0.2	-1.5	1.9	-1	-1.7	-0.3	21	17.5	24.6	27.5	23.2	32
Slovakia	2.7	-5.9	12.2	0.5	-2.7	3.8	8.6	2.7	14.9	-	-	-	-2	-3.4	-0.7	-	-	-	6.9	1.7	12.3
Slovenia	-5	-10.3	0.7	-4.7	-9.1	-0.1	16.2	10.5	22.1	0.5	-3.6	4.8	1.6	-2.6	6	3.7	-0.1	7.7	3	-0.4	6.5
Spain	0.7	-5.1	6.8	-2.5	-6.1	1.2	7.5	3.2	11.9	-2.1	-5.3	1.2	-3.5	-5.8	-1	5.5	3	8.1	6.3	3.4	9.3
Sweden	3.9	0.1	7.8	0.8	-2.4	4.1	5	-2.5	13	-1.8	-6.9	3.6	-3.4	-6.4	-0.3	4.7	2.9	6.5	9.2	4.6	13.9
Switzerland	5.7	-3.7	16.2	2.9	-3.7	9.9	7.8	0.7	15.4	0.5	-4.7	5.8	-1.7	-6.1	3	6.5	4	9	2.8	-2.3	8.2
Thailand	6.3	-3.5	17.2	0.1	-4.7	5.2	-4.9	-14.4	5.6	1.3	-2.5	5.3	-1.5	-3.8	0.9	-0.6	-2.9	1.7	0.5	-3.7	5
The Netherlands	0.5	-2.6	3.7	0.4	-3	3.9	4.9	1.4	8.4	0.4	-2.7	3.6	-1.7	-3.6	0.3	3.9	2.2	5.6	5	1.7	8.3
Turkey	1.9	-3	7	3.2	-0.1	6.6	7.8	-1.3	17.7	-1.3	-4.5	1.9	-1.7	-4	0.6	17.6	9.6	26.1	16.4	12.3	20.6
UK, England & Wales	2.5	0.8	4.2	1.7	-0.4	3.8	9.1	7.3	10.9	0.5	-1.4	2.5	-2	-3.3	-0.7	7.2	6.7	7.7	7.4	5.9	9
UK, Northern Ireland	-0.6	-6.7	5.9	3.5	-5.4	13.2	15.8	8.2	24.1	3.8	-0.8	8.6	-8.5	-14.1	-2.6	7.4	1.7	13.4	-0.6	-7.3	6.5
UK, Scotland	2.3	-1.7	6.6	-2.3	-6.3	1.9	4	-1.7	10.2	-1.4	-5.2	2.6	-2	-4.6	0.6	4.3	2	6.8	4.3	0.7	8.1
Ukraine	1.8	0.4	3.3	-1.4	-2.2	-0.7	3.2	-0.1	6.5	-4	-5.2	-2.7	-4.3	-5.1	-3.5	5.3	4	6.7	5.6	4.7	6.5
USA	2.5	1.1	3.9	-0.1	-1.8	1.6	-0.3	-2.8	2.1	2.6	1.5	3.7	0.8	-0.3	1.9	4.6	3.8	5.5	5.1	4.1	6.1
Uganda	-1	-19.3	21.5	4.6	-6.5	16.9	-6.5	-14.3	2	-12.3	-22.4	-1	-2.8	-13	8.5	7.6	-1.7	17.8	-2.2	-14.4	11.6

Trends in the incidence of 14 cancer types with increasing incidences among 20-49 year-old adults during the period of 2002-2012, by country and region. Age-standardized cancer incidence data were obtained from the Global Cancer Observatory (GLOBOCAN; https://gco.iarc.fr/). The 44 countries shown have provided age-standardized cancer incidence data during 2002-2012. Average annual percentage changes (AAPCs) with 95% confidence intervals (shown as horizontal bars) in incidence were calculated using the Joinpoint Regression Program (version 4.9.0.1) for data obtained for 2002–2012, excluding the following countries owing to differences in data availability: Costa Rica (2000–2010); Japan (2000–2010); Slovakia: (2000–2010); Spain: (2000–2010); Ukraine: (2003–2012). A maximum of two joinpoints were permitted in this analysis. Although extrahepatic bile duct cancer and gallbladder cancer (EBDC & GC) are distinct cancer types, making precise classifications is often difficult, hence, these cancer types are often recorded and data calculated together. Data were not available for the following countries: oesophageal cancer: Costa Rica (men), Poland (women), Malta (women); EBDC & GC: Uganda (men), Kuwait (men), Iceland (women), Malta (men and women); liver cancer: Malta (women); stomach cancer: Slovakia (women); thyroid cancer: Slovakia (women). AAPC, annual average percent increase; LCI, lower 95% confidence interval limit; U.K., United Kingdom; U.S.A., United States of America; UPI, upper 95% confidence interval limit.

Supplementary Table 2. Summary of studies on risk factors for early-onset breast cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Al-Ajmi et al. 2018, U.K.[1]	Prospective cohort study	273,467 females (61,903 premenopausal women and 618 premenopausal breast cancer cases)	Menarche age (years), parity, first live birth age (years), contraceptive use	RR for premenopausal breast cancer Menarche age (years): RR, 0.95 (95% CI, 0.90-1.00), parity (vs. no): RR, 0.76 (95% CI, 0.64-0.91), first live birth age (years): RR, 1.02 (95% CI, 1.00-1.05), contraceptive use (vs. no): RR, 1.26 (95% CI, 0.95-1.67)
Amadou et al. 2013, multiple countries[2]	Systematic review and meta-analysis	18 case-control studies (14,429 cases and 22,754 controls) and 11 cohort studies (5,917 cases, 1,519,500 person-years)	BMI: overall and by ethnicity	RR for premenopausal breast cancer BMI (per 5kg/ m^2), overall, Asian, African, and Caucasian: 0.95 (95% CI, 0.94-0.97), 1.05 (95% CI, 1.01-1.09), 0.95 (95% CI, 0.91-0.98), and 0.93 (95% CI, 0.91-0.95)
Band et al. 2002, Canada[3]	Case-control study	318 premenopausal breast cancer cases and 340 controls	Less than 5 years of smoking initiation from the onset of menarche	OR for premenopausal breast cancer <5 years of smoking initiation from the onset of menarche (vs. never smoking): OR, 1.77 (95% CI; 1.22-2.57)
Bergstrom et al. 2001, multiple countries[4]	Meta-analysis: 7 case control studies and 2 cohort studies (premenopausal); 9 case-control studies, 4 cohort studies (postmenopausal)	6,533 premenopausal breast cancer cases and >13,100 postmenopausal breast cancer cases	BMI	RR for premenopausal breast cancer BMI (per 1 kg/ m^2): 0.98 (95% CI, 0.97-0.99) RR for postmenopausal breast cancer: BMI (per 1 kg/ m^2): 1.02 (95% CI, 1.02-1.03)
Chan et al. 2019, multiple countries[5]	Systematic review and meta-analysis: 126 cohort studies	8.53 million women (22,900 premenopausal and 103,000 postmenopausal breast cancer cases)	Vigorous activity	RR for premenopausal breast cancer Vigorous activity (vs. no vigorous activity): RR, 0.79 (95% CI, 0.69-0.91) RR for postmenopausal breast cancer Vigorous activity (vs. no vigorous activity): RR, 0.90 (95% CI, 0.85-0.95)
Chen et al. 2011, U.S.[6]	Prospective cohort study	105,986 women (946 premenopausal breast cancer cases)	Alcohol consumption	RR for premenopausal breast cancer Alcohol consumption (vs. 0 gram/day): 0.1-4.9 g/day: RR, 0.97 (95% CI, 0.82-1.15), 5-9.9 g/day: RR, 1.15 (95% CI, 0.93-1.43), 10-19.9 g/day: RR, 1.11 (95% CI, 0.89-1.38), 20-29.9 g/day: RR, 0.96 (95% CI, 0.66-1.39), ≥30 g/day: RR, 1.35 (95% CI, 0.97-1.88), P for trend=0.03
Clavel-Chapelon et al. 2002, France[7]	Prospective cohort studies	100,000 women aged 40-65 years at baseline (1,718 breast cancer cases)	Age at menarche	RR for premenopausal breast cancer Age at menarche (vs <12 years): 12 years: RR, 0.71 (95% CI, 0.54-0.92), 13 years: RR, 0.84 (95% CI, 0.66-1.08), 14 years: RR, 0.72 (95% CI, 0.54-0.96), 15+ years: RR, 0.66 (95% CI, 0.45-0.97) RR for postmenopausal breast cancer Age at menarche (vs <12 years): 12 years: RR, 1.02 (95% CI, 0.85-1.21), 13 years: RR, 0.86 (95% CI, 0.71-1.03), RR, 14 years: RR, 0.93 (95% CI, 0.77-1.13), 15+ years: RR, 0.84 (95% CI, 0.66-1.07)

Collaborative Group on Hormonal Factors in Breast Cancer 2012, multiple countries[8]	Meta-analysis: 35 cohort studies and 82 case control studies	118,964 women with breast cancer and 306,091 without the disease	Age at menarche	RR for breast cancer (<50 years) Age at menarche (per one-year decrease): cohort studies: RR, 1.05 (95% CI, 1.02-1.07), case-control studies (population controls): RR, 1.07 (95% CI, 1.05-1.08), case-control studies (hospital controls): RR, 1.08 (95% CI, 1.06-1.10)
Collaborative Group on Hormonal Factors in Breast Cancer 1996, multiple countries[9]	Meta-analysis: 54 studies	53,297 breast cancer cases and 100,239 women without the disease	Last use of oral contraceptives <5 years ago and 5-9 years ago	RR for premenopausal breast cancer Last use of oral contraceptives (vs. never use): <5 years ago: RR, 1.22 (95% CI, 1.19-1.26), 5-9 years: RR, 1.07 (95% CI, 1.04-1.11)
Fravid et al. 2014, U.S.[10]	Prospective cohort study	88,804 women and 2,830 breast cancer	Animal fat intake	RR for premenopausal breast cancer Animal fat intake highest quintile (vs. lowest): RR, 1.21 (95% CI, 1.02-1.44)
Godinho-Mota et al. 2019, Brazil[11]	Case-control study	80 breast cancer cases and 133 controls among premenopausal women	Alcoholic habit	OR for premenopausal breast cancer Alcoholic habit (vs. no alcohol habit): OR, 2.91 (95% CI, 1.58-5.38)
Johnson et al. 2005, multiple countries[12]	Meta-analysis of 19 studies	3,000 cases, >330,000 controls for passive smoking, >188,800 controls for active smoking	Active and passive smoking	RR for premenopausal breast cancer Passive smoking (vs. not regularly exposed to tobacco smoke): RR, 1.68 (95% CI, 1.33-2.12) Active smoking (vs. not regularly exposed to tobacco smoke): RR, 2.11 (95% CI, 1.31-3.40)
Kropp et al. 2001, Germany[13]	Population-based case control study	706 breast cancer cases and 1,381 controls among women up to 50 years	Average ethanol intake	RR for breast cancer (<50 years) Average ethanol intake (vs 0 g/day): 1-5 g/day: RR, 0.71 (95% CI, 0.54-0.91), 6-11 g/day: RR, 0.67 (95% CI, 0.50-0.91), 12-18 g/day: RR, 0.73 (95% CI, 0.51-1.05), 19-30 g/day: RR, 1.10 (95% CI, 0.73-1.65), ≥31 g/day: RR, 1.94 (95% CI, 1.18-3.20)
Li et al. 2008, U.S.[14]	Population-based case-control study	4,013 breast cancer cases and 4,069 controls in White and African American women	Interval between age at menarche and age at first full-term birth	OR for premenopausal breast cancer Years between age at menarche and age at first full-term birth (vs ≤5 years), Whites: 6-10 years: OR, 1.5 (95% CI, 1.0-2.2), 11-15 years: OR, 1.5 (95% CI, 1.0-2.2), 16 years and above: OR, 1.5 (95% CI, 1.0-2.2) There were not significant results for African Americans.
Linos et al. 2010, U.S.[15]	Prospective cohort study	39, 268 premenopausal women and 455 breast cancer cases	Adolescent total fat consumption	RR for premenopausal breast cancer Total fat consumption highest quintile (vs. lowest): RR, 1.35 (95% CI, 1.00-1.81)
Lynch et al. 1988, U.S.[16]	Cross sectional study	328 probands (consecutively ascertained patients from one oncology clinic)	Family history of breast cancer diagnosed earlier than 40 years	A family history of early onset breast cancer occurred more frequently among young (<40 years) breast cancer probands (9/45) than among older (≥40 years) breast cancer probands (3/283).
Premenopausal Breast Cancer Collaborative. 2018, multiple countries[17]	Pooled analysis of 19 prospective cohorts	758, 592 women (13,082 breast cancer cases)	BMI	HR for premenopausal breast cancer (per 5 kg/m^2 increase) Breast cancer (18-24 years): HR, 0.77 (95% CI, 0.73-0.80) Breast cancer (25-34 years): HR, 0.85 (95% CI, 0.82-0.89) Breast cancer (35-44 years): HR, 0.87 (95% CI, 0.85-0.89) Breast cancer (45-54 years): HR, 0.88 (95% CI, 0.86-0.91)

Renehan et al. 2008, multiple countries[18]	Systematic review and meta-analysis: 34 datasets were included	2,559,829 women (7,930 premenopausal breast cancer cases, 23,909 postmenopausal breast cancer cases)	BMI	RR for premenopausal breast cancer BMI (per 5kg/ m^2): overall: 0.92 (95% CI, 0.88-0.97), North America: 0.91 (95% CI, 0.85-0.98), Europe and Australia: 0.89 (95% CI, 0.84-0.94), and Asia-Pacific: 1.16 (95% CI, 1.01-1.32) RR for postmenopausal breast cancer BMI (per 5kg/ m^2): all: 1.12 (95% CI, 1.08-1.16), North American: 1.15 (95% CI, 1.08-1.23), Europe and Australia: 1.09 (95% CI, 1.04-1.14), and Asia-Pacific: 1.31 (95% CI, 1.15-1.48)
Rosner et al. 2017, U.S.[19]	Prospective cohort study	74,177 nurses and 4,965 breast cancer cases	Weight at age 18	HR for premenopausal breast cancer: Weight (per 30 kg): 0.52 (95% CI, 0.39-0.71) HR for postmenopausal breast cancer Weight (per 30 kg): 0.81 (95% CI, 0.72-0.92)
Ursin et al. 1995, multiple countries[20]	Meta-analysis: 19 case control studies and 4 cohort studies	Premenopausal women	BMI	RR for premenopausal breast cancer BMI (per 8kg/ m^2) in cohort studies: RR, 0.70 (95% CI, 0.54-0.91),
van den Brandt et al. 2021, multiple countries[21]	Pooled analysis of 20 prospective cohort studies	1,061,915 women (36,297 breast cancer cases)	Height	RR for premenopausal breast cancer: Height (per 5cm): 1.07 (95% CI, 1.04-1.10) RR for postmenopausal breast cancer: Height (per 5cm): 1.06 (95% CI, 1.05-1.08)
van den Brandt et al. 2017, Netherlands[22]	Prospective cohort study	62,573 women and 3,354 breast cancer cases	Smoking duration	HR for breast cancer: Smoking duration before menopause (per 20 pack-years): 1.35 (95% CI, 1.10-1.65) HR for postmenopausal breast cancer: Smoking duration after menopause (per 20 pack-years): 0.47 (95% CI, 0.28-0.80)
van den Brandt et al. 2000, multiple countries[23]	Meta-analysis: 7 prospective cohort studies	337,819 women (4,385 breast cancer cases)	BMI	RR for premenopausal breast cancer: BMI (per 4kg/ m^2): 0.89 (95% CI, 0.81-0.97) RR for postmenopausal breast cancer BMI (per 4kg/ m^2): 1.07 (95% CI, 1.02-1.11)
World Cancer Resarch Fund, 2020, multiple countries[24]	Meta-analysis: 10 studies	4227 breast cancer cases	Alcohol consumption	RR for premenopausal breast cancer: Alcohol consumption (per 10 g/day): 1.05 (95% CI, 1.02-1.08)
Xiao et al. 2019, multiple countries[25]	Systematic review and meta-analysis: 14 cohort and 18 case-control studies	Premenopausal and postmenopausal women	Western dietary pattern	RR for premenopausal breast cancer Western dietary pattern (vs. no western dietary pattern): RR, 1.18 (95% CI, 0.99-1.40) RR for postmenopausal breast cancer Western dietary pattern (vs. no western dietary pattern): RR, 1.20 (95% CI, 1.06-1.35)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Supplementary Table 3. Summary of studies on risk factors for early-onset colorectal cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Ali Khan et al. 2020, Sweden[26]	Descriptive analysis of cohort data	12,614,256 individuals; 559,375 diabetic patients; 162,226 CRC patients (<50 years)	Type 2 diabetes	Early-onset vs. late-onset sporadic cancer Diabetes diagnosis (vs. no diabetes): SIR, 1.9 (95% CI, 1.6-2.3) vs. SIR, 1.6 (95% CI, 1.6-1.7) Early-onset vs. late-onset cancer with 1 first-degree relative: SIR (95% CI) Diabetes diagnosis (vs. no diabetes): SIR,6.9 (95% CI, 4.1-12) vs. SIR,1.9 (95% CI, 1.4-2.5) Cumulative risk for young-onset CRC Diabetic patients: 0.3% (95% CI, 0.3%-0.3%) for sporadic CRC and 1.7 % (95% CI, 0.3%-3.1%) for CRC with 1 a first-degree relative
Archambault et al. 2021, multiple countries[27]	Case-control study	3,767 CRC cases and 4,049 controls aged younger than 50 years and 23,437 CRC cases and 35,311 controls aged 50 years and older	Lifestyle factors	OR for early-onset CRC Nonsteroidal anti-inflammatory drugs: OR, 1.43 (95% CI, 1.21–1.68) lower educational attainment: OR, 1.10 (95% CI, 1.04–1.16) alcohol abstinence: OR, 1.23 (95% CI, 1.08–1.39) heavier alcohol use: OR, 1.25 (95% CI, 1.04–1.50)
Archambault et al. 2020, U.S.[28]	Cross-sectional analysis	108,062 participants (50,023 CRC cases and 58,039 controls)	Genetic risk variants (polygenic risk score (PRS) from 95 CRC associated common genetic risk variants)	OR for CRC (per SD of PRS) Entire sample: OR, 1.73 (95% CI, 1.54–1.95) for CRC <50 years, OR, 1.47 (95% CI, 1.37–1.58) for CRC >50 years Excluding Lynch cases: OR, 1.82 (1.61–2.06) for CRC <50 years, OR, 1.49 (95% CI, 1.39–1.60) for CRC >50 years
Breau et al. 2020, multiple countries[29]	Review and a meta-analysis of 5 studies		Smoking, alcohol, obesity, elevated blood glucose, elevated blood pressure, elevated triglycerides	OR for early-onset adenoma and CRC Smoking: OR, 1.69 (95% CI, 1.44-1.99), alcohol consumption: OR, 1.48 (95% CI, 1.40-1.57), obesity: OR, 1.45 (95% CI, 1.38-1.53), elevated blood glucose: OR, 1.69 (95% CI, 1.27-2.25), elevated blood pressure: OR, 1.56 (95% CI, 1.31-1.86), elevated triglycerides: OR, 1.51 (95% CI, 1.41-1.62)
Buc et al. 2006, France[30]	Cross-sectional study	852 CRC cases (209 cases aged <60 years vs. 643 cases aged ≥60 years)	Smoking	OR for CRC (<60 years) Tobacco smoking at least an average of 10 pack/years (yes vs. no): OR, 2.49 (95% CI, 1.57-3.95).
Chen et al. 2021, U.S.[31]	Nested case-control study	4,673 early-onset CRC cases and 40,832 controls vs. 14,928 CRC (50-64 years) and 132,120 matched controls	Metabolic syndrome	OR for early-onset CRC Metabolic syndrome (vs. no): OR, 1.25 (95% CI, 1.09-1.43), number of metabolic comorbid conditions (vs. 0): 1: OR, 1.15 (95% CI, 1.06-1.24), 2: OR, 1.22 (95% CI, 1.10-1.35), ≥3: OR, 1.15 (95% CI, 1.06-1.24), per 1 condition: OR, 1.12 (95% CI, 1.08-1.16)
Chen et al. 2017, U.S.[32]	Cross-sectional study	485 colorectal adenomas (<50 years, N=253 vs. >50 years, N=232)	Family history, hereditary factor	Early-onset vs. late-onset Family history of CRC: 24.9% vs. 16.8%, P<0.03, confirmed or probable hereditary cancer syndromes: 6.7% vs. 0.86%, P<0.01
Chung et al. 2010, Korea[33]	Cross-sectional study	5,254 asymptomatic subjects who underwent screening colonoscopy (30-39 years, N=608, 40-	Current smoking, family history (CR advanced adenoma <50 years)	OR for low risk adenoma (30-39 years) current smoker (vs. never): OR, 2.05 (95% CI, 1.16-3.65), BMI (vs. <35.0kg/m^2): OR, 0.68 (95% CI, 0.31-1.48) OR for low risk adenoma (40-49 years)

		49 years, N=1,930, 50-59 years, N=2,716)		current smoker (vs. never): OR, 1.37 (95% CI, 1.06-1.79), BMI (vs. <35.0kg/m^2): OR, 0.82 (95% CI, 0.61-1.12) OR for low risk adenoma (50-59 years) current smoker (vs. never): OR, 1.56 (95% CI, 1.24-1.95), BMI (vs. <35.0kg/m^2): OR, 1.47 (95% CI, 1.20-1.79) OR for advanced adenoma (40-49 years) current smoker (vs. never): OR, 1.58 (95% CI, 1.06-3.50), family history of CRC: OR, 2.54 (95% CI, 1.16-5.56) OR for advanced adenoma (50-59 years) current smoker (vs. never): OR, 2.03 (95% CI, 1.30-3.17), family history of CRC: OR, 1.53 (95% CI, 0.95-2.45)
Elangovan et al. 2020, U.S.[34]	Cross-sectional study	CRC (<50 years) cases vs. controls: 20-39 years: 11,930 vs. 9,471,990 40-49 years: 4160 vs. 4,413,690 50-74 years: 62,800 vs. 11,651,380	Obesity, type 2 diabetes, hypertension, hyperlipidemia, smoking	CRC diagnosed at 20-39 years, men obesity: OR, 1.92 (95% CI, 1.85-1.99), type 2 diabetes: OR, 3.42 (95% CI, 2.85-5.37), hypertension: OR, 3.43 (95% CI, 2.77-4.22), hyperlipidemia: OR, 3.42 (95% CI, 2.48-4.04), and smoking: OR, 1.77 (95% CI, 1.43-2.15) CRC diagnosed at 20-39 years, women obesity: OR, 2.22 (95% CI, 1.84-2.43), and hyperlipidemia: OR, 2.37 (95% CI, 2.22-2.52) CRC diagnosed at 40-49 years, men obesity: OR, 1.96 (95% CI, 1.87-1.99), type 2 diabetes: OR, 2.00 (95% CI, 1.75-1.99), hypertension: OR, 2.00 (95% CI, 1.85-2.15), hyperlipidemia: OR, 1.50 (95% CI, 1.35-1.67), smoking: OR, 1.25 (95% CI, 1.16-1.36) CRC diagnosed at 20-39 years, women obesity: OR, 1.49 (95% CI, 1.41-1.57), hypertension: OR, 1.27 (95% CI, 1.13-1.42), hyperlipidemia: OR, 1.47 (95% CI, 1.32-1.63), smoking: OR, 1.92 (95% CI, 1.85-1.99)
Fraser et al 1993, New Zealand[35]	Cross-sectional study	1,651 colon cancer and 1,046 rectal cancer aged 15-64 years	Occupational physical activity (sedentary, intermediate vs. high)	RR for colon cancer Sedentary (vs. high activity): RR, 1.01 (0.45-2.30) for colon cancer diagnosed at 15-34 years, RR, 1.79 (95% CI, 1.21-2.63) for colon cancer diagnosed at 35-44 years, and RR,1.45 (1.12-1.88) for colon cancer diagnosed at 45-54 years old RR for rectal cancer Sedentary (vs. high activity): RR, 2.85 (95% CI, 1.15-7.08) for rectal cancer diagnosed at 15-34 years, RR,1.26 (95% CI, 0.69-2.31) for rectal cancer diagnosed at 35-44 years, and RR, 1.47 (95% CI, 1.04-2.08) for rectal cancer diagnosed at 45-54 years old
Fuchs et al. 1994, U.S.[36]	Cross-sectional study	32,085 men and 87,031 women (CRC: 148 men and 315 women, <50 years)	First degree relatives	RR for early-onset CRC First degree relatives (vs. no family history): CRC 30-44 years: RR, 4.63 (95% CI, 1.43-15.0), CRC 45-49 years: RR, 3.47 (95% CI, 1.62-7.44) Female: CRC 30-44 years: RR, 4.66 (95% CI, 1.24-17.4), CRC 45-49 years: RR, 4.15 (95% CI, 1.83-9.44) Male: No categories were not statistically significant.
Gausman et al. 2020, U.S.[37]	Case-control study	269 patients with early-onset CRC vs. 2,802 with late-onset vs.1122 controls	Family history of CRC, BMI, hyperlipidemia	CRC cases vs. control: OR Family history of CRC: OR, 8.61 (95% CI, 4.83-15.75), hyperlipidemia: OR, 0.57 (95% CI, 0.38-0.83) Early-onset vs. late-onset CRC: OR Family history of CRC: OR, 2.87 (95% CI, 1.89-4.25), BMI (kg/m^2): OR, 0.98

				(95% CI, 0.95-0.99)
Giráldez et al. 2012, Spain[38]	Cross-sectional analysis	191 early onset cancer vs. 1264 late onset cancer (>65 years)	Genetic risk factor	<50 years vs. > 65 years: OR In dominant inheritance model, risk allele carriers for rs3802842 (vs. no carriers): OR, 1.5 (95% CI, 1.1–2.05), P = 0.0096 and rs4779584 (vs. no carriers): OR, 1.39 (95% CI, 1.02–1.9), P = 0.0396 In codominant and additive inheritance model, homozygotes for rs10795668 risk allele vs. no carrier: 10.53% vs. 8.63 %, P= 0.02
Hall et al. 1996, U.K.[39]	Cross-sectional study	60 CRC cases (<45 years) and 200 CRC cases (all ages)	First degree relative	CRC aged (<45 years): RR, 5.2 (p<0.0001) CRC at all ages: RR, 2.3 (p<0.0001)
Heikkinen 2020, Finland[40]	Descriptive analysis using prospective cohort data	20,536 relatives of early-onset cancer patients (≤ 40 years)	Family history	SIR for early-onset CRC (≤ 40 years) relative to the general population All first-degree relatives: SIR, 14 (95% CI, 9.72-18), offspring: SIR,13 (95% CI, 7.20-21), father: SIR, 20 (95% CI, 7.21-43), mother: SIR, 14 (95% CI, 3.72-35), sibling: SIR,13 (95% CI, 7.34-21) Cumulative risk for offspring and sibling vs. population 1.37% (95% CI, 0.83-2.25%), 0.98% (95% CI, 0.58-1.64%) vs. 0.10%
Hong et al. 2010, Korea[41]	Cross-sectional study	1,049 people who underwent their first colonoscopy screening (40-49 years: N=1,049 (CRC or adenoma =181) vs. 50-59 years: N=712 (CRC or adenoma=158)	BMI, abdominal obesity, metabolic syndrome	OR for overall CRC or adenoma, age 40-49 BMI, 23.0-24.9 and ≥25 kg/m$_2$ (vs. >23.0): OR, 1.24 (95% CI, 0.82-1.87) and OR, 1.31 (95% CI, 0.87-1.97), abdominal obesity (vs.no): OR, 1.57 (95% CI, 1.12-2.21), metabolic syndrome (vs. no): OR, 1.56 (95% CI, 1.03-2.35) OR for overall CRC or adenoma, 50-59 years BMI, 23.0-24.9 and ≥25 kg/m$_2$ (vs. >23.0): OR, 1.25 (95% CI, 0.80-1.97) and OR, 1.09 (95% CI, 0.70-1.70), abdominal obesity (vs.no): OR, 1.04 (95% CI, 0.72-1.50) OR for advanced CRC or adenoma, age 40-49 BMI, 23.0-24.9 and ≥25 kg/m$_2$ (vs. >23.0): OR, 1.69 (95% CI, 0.56-5.05) and OR, 2.12 (95% CI, 0.76-5.97), abdominal obesity: OR, 2.37 (95% CI, 1.06-5.27), metabolic syndrome: OR, 2.83 (95% CI, 1.23-6.53) OR for advanced CRC or adenoma, age 50-59 years BMI, 23.0-24.9 and ≥25 kg/m$_2$ (vs. >23.0): OR, 1.72 (95% CI, 0.65-4.57) and OR, 1.63 (95% CI, 0.63-4.23), abdominal obesity: OR, 1.14 (95% CI, 0.54-2.40), metabolic syndrome: OR, 1.39 (95% CI, 0.64-3.00)
Hur et al. 2021, U.S.[42]	Prospective cohort study	95,464 women (109 early-onset CRC, 1,358,142 person years	Sugar-sweetened beverage intake in adulthood and adolescence	RR for early-onset CRC Sugar sweetened beverages ≥2 servings/day (vs. <1 serving/week) in adulthood: RR, 2.18 (95% CI, 1.10-4.35), artificially sweetened beverages ≥2 servings/day (vs.<1 serving/week): RR, 0.73 (95% CI, 0.42-1.27), fruit juice ≥2 servings/day (vs. <1 serving/week): RR,1.20 (95% CI, 0.16-9.11) Sugar sweetened beverages ≥2 servings/day (vs.<1 serving/week) in adolescence: RR, 3.41 (95% CI, 1.08-10.8)
Hussan et al. 2020, U.S.[43]	Analysis of population-based program data	91,116 (7.2%) obese individuals vs. 1,181,127 (92.8%) nonobese individuals	Obesity	AAPC of cancer incidence: 20-49, 50-64, 65-74, and 75+ years Overall CRC: +1.5, -1.5, -3.8, and -3.9, cancer resection with obesity vs. without obesity: +13.1, +10.3, +11.3 and +12.8 vs. -1.1, -1.0, -3.0, and -4.0
Jung et al. 2017, Korea[44]	Cross-sectional study	CRC or advanced adenoma=56,896 vs.	BMI, former smoker, current smoker	OR for CRC or advanced adenoma BMI (≥ 25 kg/m2): OR, 1.04 (95% CI, 1.08-1.07), former smoker and current

		control=739		smoker (vs. never smoker): OR, 1.24 (95% CI, 0.99-1.55) and OR, 1.09 (95% CI, 1.56-2.32)
Jung et al. 2015, Korea[45]	Cross-sectional study	Total 26,185 persons who had undergone a colonoscopy aged 30-59 years (13,678 aged 30-39 years, 12,507 aged 40-49 years)	Smoking, metabolic syndrome, obesity, fasting blood glucose, triglyceride level	OR for overall CRC or adenoma (30-39 years) Smoking 0-20 and ≥ 20 (vs. never smoker): OR, 1.43 (95% CI, 1.23-1.66) and OR, 1.93 (95% CI, 1.34-2.77), metabolic syndrome: OR, 1.43 (95% CI, 1.21-1.69), obesity (≥ 25.0 kg/m^2) (vs. <25 kg/m^2): OR, 1.33 (95% CI, 1.16-1.54), fasting blood glucose (vs. <100 mg/dL): OR, 1.36 (1.17-1.57), elevated triglyceride levels (vs. <150 mg/dL): OR, 1.41 (95% CI, 1.22-1.64) OR for overall CRC or adenoma (40-49 years) Smoking 0-20 and ≥ 20 (vs. never smoker): OR, 1.16 (95% CI, 1.03-1.31) and OR, 1.54 (95% CI, 1.33-1.78), metabolic syndrome: OR, 1.22 (95% CI, 1.09-1.37), obesity (≥ 25.0 kg/m^2) (vs. <25 kg/m^2): OR, 1.19 (95% CI, 1.07-1.32), fasting blood glucose (vs. <100 mg/dL): OR, 1.15 (95% CI, 1.04-1.28), elevated triglyceride levels (vs. <150 mg/dL): OR, 1.20 (1.08-1.34) OR for advanced CRC (30-39 years) Smoking ≥ 20 (vs. never smoker): OR, 4.42 (95% CI, 1.80-10.80), elevated triglyceride levels (vs. <150 mg/dL): OR, 2.00 (95% CI, 1.26-3.16) OR for advanced CRC (40-49 years) Smoking ≥ 20 (vs. never smoker): OR, 1.64 (95% CI, 1.14-2.37), metabolic syndrome: OR, 1.38 (95% CI, 1.05-1.81), obesity (≥ 25.0 kg/m^2) (vs. <25 kg/m^2): OR, 1.35 (95% CI, 1.05-1.74)
Kim at al. 2021, U.S.[46]	Prospective cohort study	94,205 women (111 early-onset CRC, 1,250,560 person years)	Total vitamin D intake	RR for early-onset CRC Total vitamin D intake (vs. <300 IU/day): 300-450 IU/day, HR, 0.51 (95%CI, 0.30-0.86), ≥450 IU/day, HR, 0.49 (95%CI, 0.26-0.93) Total vitamin D intake (per 400 IU/day): HR, 0.46 (95%CI, 0.26-0.83)
Kim et al. 2019, Korea[47]	Cross-sectional study	72,356 asymptomatic individuals, 20-39 years who underwent colonoscopies (20-29 years, N=7,340, 30-39 years, N=65,016)	Smoking, alcohol, obesity, metabolic syndrome (abdominal obesity, increased total triglycerides, increased blood pressure, fasting blood glucose)	OR for colorectal neoplasm (cancer and adenoma) (20-29 years) Smoking: OR, 1.14 (95% CI, 0.90-1.43), alcohol intake ≥20 g/d (vs. >20 g/day): OR, 1.16 (95% CI, 0.91-1.48), obesity (BMI ≥25.0 kg/m^2): OR, 1.46 (95% CI, 1.17-1.82), metabolic syndrome: OR, 1.45 (95% CI, 0.92-2.27), abdominal obesity: 1.45 (95% CI, 1.14-1.84), elevated blood pressure: OR, 1.65 (95% CI, 1.19-2.29), elevated fasting glucose level: OR, 2.99 (95% CI, 1.38-6.45), elevated total triglycerides level: OR, 1.49 (95% CI, 1.12-1.97), reduced HDL: OR, 1.22 (95% CI, 0.87-1.72) OR for colorectal neoplasm (cancer and adenoma) (30-39 years) Smoking: OR, 1.29 (95% CI, 1.21-1.38), alcohol intake ≥20 g/d (vs >20 g/day): OR, 1.25 (95% CI, 1.17-1.33), obesity (BMI ≥25.0 kg/m^2): 1.26 (95% CI, 1.19-1.34), metabolic syndrome: OR, 1.33 (95% CI, 1.21-1.46), abdominal obesity: OR, 1.32 (95% CI, 1.23-1.40), elevated blood pressure: OR, 1.25 (95% CI, 1.16-1.35), elevated fasting glucose level: OR, 1.23 (95% CI, 1.00-1.52), elevated total triglycerides level: OR, 1.24 (95% CI, 1.16-1.33), reduced HDL: OR, 1.08 (95% CI, 1.00-1.17) OR for advanced colorectal neoplasm (cancer and adenoma) (20-29 years) Obesity (BMI ≥25.0 kg/m^2): OR, 2.46 (95% CI, 1.24-4.87), abdominal obesity: 2.26 (95% CI, 1.12-4.54), elevated total triglycerides level: OR, 2.95 (95% CI, 1.41-6.21) OR for advanced colorectal neoplasm (cancer and adenoma) (30-39 years)

				Smoking: OR, 1.30 (95% CI, 1.05-1.61), alcohol intake ≥20 g/d (vs. >20 g/day): OR, 1.34 (95% CI, 1.10-1.63), obesity (BMI ≥25.0 kg/m^2): 1.33 (95% CI, 1.11-1.61), abdominal obesity: OR, 1.28 (95% CI, 1.05–1.57)
Kim et al. 2019, Korea[48]	Retrospective cross-sectional study	41,702 asymptomatic people who underwent screening aged younger than 49 years old (393 advance colorectal neoplasm)	Alcohol consumption, smoking, obesity, glucose metabolism abnormality	OR for colorectal neoplasm (cancer and adenoma) Heavy drinker (vs. never or non-heavy drinker): OR, 1.40 (95% CI, 1.13-1.74), current smokier (vs. never or former smoker): OR, 1.41 (95% CI, 1.14-1.75), obesity (vs. non-obesity): OR, 1.29 (95% CI, 1.04-1.59), HbA1c ≥ 6.5% or glucose ≥ 100 mg/dL (vs. no): OR, 1.55 (95% CI, 1.24-1.93).
Kim et al. 2016, Korea[49]	Cross-sectional study	A total of 70,428 Koreans from an occupational cohort (<50 years, N=59,782, ≥50 years, N= 10,646)	Smoking, family history, diabetes related factors (fasting plasma glucose ≥100 mg/dl or hemoglobin A1c ≥6.5%, or use of diabetes medications), obesity, carcinoembryonic antigen, LDL-cholesterol	HR for colorectal neoplasm (cancer and adenoma) <50 years Current smoking (vs. never/former smoking): OR, 1.37 (95% CI, 1.15-1.63), family history of CRC: OR, 1.46 (95% CI, 1.01-2.10, diabetes related factors: OR, 1.27 (95% CI, 1.06-1.54), obesity: OR, 1.23 (95% CI, 1.03-1.47), carcinoembryonic antigen: OR, 1.04(95% CI, 1.01-1.09), LDL-cholesterol: OR, 1.01 (95% CI, 1.01-1.02) HR for colorectal neoplasm (cancer and adenoma) <50 years, female Age (per one year increase): OR, 1.08 (95% CI, 1.04-1.11), carcinoembryonic antigen (vs. no): OR, 1.12 (95% CI, 1.02-1.23) HR for colorectal neoplasm (cancer and adenoma) <50 years, male Age (per one year increase): OR, 1.09 (95% CI, 1.07-1.10), current smoking (vs. never/former smoking): OR, 1.54 (95% CI, 1.27-1.87), family history of CRC: OR, 1.58 (95% CI, 1.06-2.36), diabetes related factors: OR, 1.34 (95% CI, 1.09-1.65), obesity: OR, 1.24 (95% CI, 1.02-1.50), LDL-cholesterol: OR, 1.01 (95% CI, 1.01-1.02), carcinoembryonic antigen (vs. no): OR, 1.03 (95% CI, 1.01-1.05)
Kwak et al. 2016, Korea[50]	Cross-sectional study	Asymptomatic young adults aged 20-39 years - Subjects with colorectal adenoma (N =497) - Subject without colorectal adenoma (N =3,789)	Current smoking, alcohol consumption, obesity, abdominal obesity, elevated blood pressure, fasting glucose, triglyceride, HDL, metabolic syndrome	OR for adenoma (20-39 years) Current smoker (vs. nonsmoker): OR, 1.48 (95% CI, 1.14-1.91), alcohol consumption (vs. ≤ 40g /day): OR, 1.29 (95% CI, 1.03-1.63), obesity ≥ 25 kg/m2 (vs. <25 kg/m2): OR, 1.03 (95% CI, 0.78-1.35), waist ≥ 90cm in men or ≥80 in women): OR, 1.06 (95% CI, 0.79-1.43), elevated blood pressure: OR, 1.06 (95% CI, 0.84-1.33), elevated fasting glucose: OR, 1.32 (95% CI, 0.91-1.92), Elevated triglycerides: OR, 0.91 (95% CI, 0.68-1.23), reduced HDL: OR, 1.26 (95% CI, 0.91-1.75), metabolic syndrome: OR, 0.94 (95% CI, 0.59-1.48)
Lee et al. 2016, Korea[51]	Cross-sectional study	2,819 subjects aged <50 years (non-adenoma, N=2264 vs. adenoma, N=555)	Waist circumference, current smoking, current alcohol consumption	OR for colorectal adenoma Waist circumference: ≥90 cm for male, ≥80 cm for female (vs. <90 cm, <80cm, respectively): OR, 1.72 (95% CI, 1.15-2.55), Current smoking (vs. never smoker): OR, 1.6 (95% CI, 1.07-2.41) OR for colorectal advanced adenoma Current alcohol consumption: OR, 3.69 (95% CI, 1.08-12.54)

Levi et al. 2017, Israel[52]	Prospective cohort study	1,794,570 adolescents who underwent compulsory examinations in late adolescence	Adolescent BMI (US CDC criteria) -underweight: <5th -healthy weight: 5th-85th -overweight: 85th-95th -obese: >95th	HR for CRC ≤35 years Underweight, overweight, and obese (vs. healthy weight): HR, 1.45 (95% CI, 1.03-2.06), HR,1.56 (95% CI, 1.13-2.15), HR,1.11 (95% CI, 0.61-2.03) HR for CRC 36-45 years Underweight, overweight, and obese (vs. healthy weight): HR,1.21 (95% CI, 0.91-1.60), HR,1.35 (95% CI, 1.04-1.76), HR, 1.58 (95% CI, 1.02-2.44) HR for CRC >45 years Underweight, overweight, and obese (vs. healthy weight): HR, 0.92 (95% CI, 0.75-1.13), HR,1.39 (95% CI, 1.18-1.62), HR,1.74 (95% CI, 1.33-2.27)
Liu et al. 2019, U.S.[53]	Prospective cohort study	85,256 women (114 cases of early-onset CRC), 1,196, 452 person-years of follow-up	BMI	RR for early-onset CRC Current BMI 25.0-29.9 and ≥30 (vs.18.5-22.9 kg/m^2): RR,1.37 (95% CI, 0.81-2.36) and RR,1.93 (95% CI, 1.15-3.25), 5 unit increase of BMI: RR,1.20 (95% CI, 1.05-1.38) (P =0.01 for trend), BMI at 18 years 25.0-29.9 and ≥30 (vs.18.5-22.9 kg/m^2): RR, 1.32 (95% CI, 0.80-2.16) and RR, 1.63 (95% CI, 1.01-2.61), 5 unit increase of BMI at 18 years: RR, 1.06 (95% CI, 0.81-1.40), weight gain of 20-39.9 kg, ≥40 kg (vs. loss or gain <5.0 kg) since 18 years: RR,1.65 (95% CI, 0.96-2.81), RR, 2.15 (95% CI, 1.01-4.55), 5 kg increase of weight since 18 years: RR, 1.09 (95% CI, 1.02-1.16)
McDowell et al. 2021, Sweden[54]	Case-control studies	7,903 CRC cases (including 445 early-onset CRC cases) and 30,418 controls	Antibiotics use	OR for early-onset colon cancer Antibiotics use (vs. no use): HR, 1.49 (95% CI, 1.07-2.07)
Nguyen et al. 2022, Sweden.[55]	Case-control study	54,804 cases of CRC (2,557 early-onset CRCs) and 261,089 controls	Sedentary TV viewing time	OR for early-onset CRC Previous antibiotics use: OR, 1.06 (95% CI, 0.96-1.17)
Nguyen et al. 2018, U.S.[56]	Prospective cohort study	116,430 female nurses ages 25-42 years at enrollment in 1989 [118 early-onset CRC (<50 years)]	Sedentary TV viewing time	RR for early-onset CRC Viewing time, 7.1-14 hours and >14 hours/week (vs. ≤7 hours): RR, 1.12 (95% CI, 0.72-1.75) and RR, 1.69 (95% CI, 1.07-2.67), P_{trend} =0.03 Individuals without CRC family history: RR, 0.99 (95% CI, 0.61-1.61) and RR, 1.83 (95% CI, 1.15-2.95), P_{trend} =0.02
O'Sullivan et al. 2021, multiple countries[57]	Systematic review and a meta-analysis: 20 studies were included		CRC history in a first-degree relative, hyperlipidemia, obesity, alcohol consumption, and smoking	RR for early-onset CRC CRC history in a first-degree relative (vs.no): RR, 4.21 (95% CI, 2.61-6.79), hyperlipidemia (vs.no): RR, 1.62 (95% CI, 1.22-2.13), Obesity (vs. normal): RR, 1.54 (95% CI, 1.01-2.35), high alcohol consumption (vs. non-drinkers): RR, 1.71 (95% CI, 1.62-1.80), smoking (vs. never smoking): RR, 1.35 (95% CI, 0.81-2.25)
Pearlman et al. 2017, U.S.[58]	Cross-sectional study	450 patients diagnosed with CRC diagnosed <50 years	Gene mutation	Prevalence of mutation: % Any pathogenic mutation: 72 (16%), Mismatch repair (MMR)-deficient tumors: 48 (10.7%), Lynch syndrome: 36 (8%), high or moderate penetrance gene mutation: 61 (13.6 %), low penetrance gene mutation: 11 (2.4%)
Peters et al 1989, U.S.[59]	Case-control study	147 colorectal adenocarcinoma cases in white males <45 years old at diagnosis vs. 148 controls	Occupational physical activity	OR for transverse/descending colon cancer Mainly sedentary (vs. moderately active): OR, 3.0 (95% CI, 1.2-7.2), very active (vs. moderately active): OR, 0.8 (95% CI, 0.2-2.7).

Rosato et al. 2013, Switzerland and Italy[60]	Case-control study	329 cases (≤45 years) and 1,361 controls	Family history, alcohol consumption, food consumption, micronutrient, diabetes	OR for CRC (≤45 years) Family history in first-degree relatives (vs.no family history): OR, 4.5 (95% CI, 2.64-7.68), affected siblings (vs. no family history): OR 11.68 (95% CI, 2.97-45.9), alcohol ≥14 drinks/weeks: OR, 1.56 (95% CI, 1.12-2.16), 3rd tertile of processed meat, vegetables, fruit, and fish intake (1st tertile): OR, 1.56 (95% CI, 1.11-2.20), OR, 0.4 (95% CI, 0.28-0.56), OR, 0.75 (95% CI, 0.54-1.02), and OR, 0.78 (95% CI, 0.60-1.00), respectively, Beta carotene, vitamin C, vitamin E, and folate: OR, 0.52 (95% CI, 0.37-0.72), OR, 0.68 (95% CI, 0.49-0.94), OR, 0.38 (95% CI, 0.26-0.58), and OR, 0.59 (95% CI, 0.40-0.86), respectively.
Sanford et al. 2020, U.S.[61]	Cross-sectional study	583,511 noninstitutionalized civilian adults, of which 321,975 were aged between 18-49 years	Obesity, ethnicity	Entire sample including age ≥ 50 years Interaction term of age and BMI: OR, 0.67 (95% CI, 0.47-0.94). Early-onset CRC vs. late-onset CRC: OR Non-Spanish Hispanic Latino (vs. Spanish Hispanic Latino): OR, 2.03 (95% CI, 1.07–3.84) vs. OR, 1.74 (95% CI, 1.43–2.11), BMI ≥30.0 kg/m^2 (vs.<30): OR, 1.39 (95% CI, 1.00-1.92) vs. OR, 0.93 (95% CI, 0.85-1.03), current and former smoker (vs. non-smoker): OR, 1.51(95% CI, 1.10-2.08) vs. OR, 1.31 (95% CI, 1.20-1.43)
Song et al. 2021, Sweden[62]	Case-control study	45,744 polyp cases (including 7,884 early-onset CRC cases) and 93,307 controls (15,837 controls for early-onset cases)	Antibiotics use	OR for colorectal polyps Narrow-spectrum antibiotics (vs. no use): OR, 0.88 (95% CI, 0.78-0.88), broad-spectrum antibiotics (vs. no use): OR, 1.29 (95% CI, 1.14-1.45), Penicillin (vs. no use): OR, 0.87 (95% CI, 0.78-0.98), Tetracyclines (vs. no use): OR, 1.24 (95% CI, 1.08-1.42), Quinolones (vs. no use): OR, 1.33 (95% CI, 1.09-1.62), Sulfonamides and trimethoprim (vs. no use): OR, 1.37 (95% CI, 1.08-1.75), Cephalosporins and other non-penicillin beta-lactams (vs. no use): OR, 1.30 (95% CI, 1.05-1.61)
Stoffel et al. 2018, U.S.[63]	Retrospective chart review	430 individuals diagnosed with CRC age<50	Germline mutation	Prevalence of mutation: % Mismatch repair deficiency: 41/430 (10%), Lynch syndrome: 56/315 (those who underwent clinical germline sequencing) (25 with mutations in *MSH2*, 24 with mutations in *MLH1*, 5 with mutations in *MSH6*, and 2 with mutations in *PMS2*).
Syed et al 2019, U.S.[64]	Case-control study	CRC <50 years (N=5,710), CRC ≥ 50 years (N=63,010), and control without CRC (N=11,800,420)	Family history, tobacco use, alcohol use, hyperlipidemia, obesity	CRC <50 years vs. ≥50 years: OR Obesity: OR, 1.14 (95% CI, 1.08-1.20), tobacco use: OR, 0.83 (95% CI, 0.79-0.88), alcohol use: OR, 0.83 (95% CI, 0.78-0.88), family history: OR, 1.78 (95% CI, 1.67-1.90), hyperlipidemia: OR, 0.20 (95% CI, 0.19-0.22), hypertension: OR, 0.22(95% CI, 0.21-0.23) CRC <50 years vs. control: OR Family history of cancer: OR, 11.66 (95% CI, 10.97-12.39), tobacco use: OR, 2.46 (95% CI, 2.33-2.59), alcohol use: OR, 1.71 (95% CI, 1.62-1.80), obesity: OR, 2.88 (95% CI, 2.74-3.04), hypertension: OR, 2.86 (95% CI, 2.70-3.03), hyperlipidemia: OR, 2.39 (95% CI, 2.23-2.55)
Win et al 2011, multiple countries[65]	Prospective cohort study	Carriers of pathogenic mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* (659 cases and 655 control)	BMI at 20 years old, CRC (mean age at CRC diagnosed=44.0, SD, 11.1)	HR for CRC BMI (per 5 kg/m^2 increase): HR, 1.30 (95% CI, 1.08-1.58), underweight, overweight, and obese (vs. normal weight): HR, 1.04 (95% CI, 0.66-1.64), HR, 1.12 (95% CI, 0.78-1.62), and HR, 2.35 (95% CI, 1.30-4.23)

Yue et al. 2021, U.S.[66]	Prospective cohort study	94,217 women aged 26-45 years at baseline and total 332 CRC cases (111 CRC <50 years and 222 CRC ≥50 years)	Hyperinsulinemic lifestyle: prime diet quality score, plant-based diet indices, empirical dietary index for hyperinsulinemia, empirical lifestyle Index for hyperinsulinemia. All was categorized into quartiles.	HR for CRC <50 years vs. ≥50 years Prime diet quality score: HR, 0.90 (95% CI, 0.55-1.50) plant-based diet indices: HR,1.24 (95% CI, 0.74-2.08), empirical dietary index for hyperinsulinemia: HR, 1.24 (95% CI, 0.72-2.16), empirical lifestyle Index for hyperinsulinemia: HR,1.86 (95% CI, 1.12-3.07) HR for CRC ≥50 years Prime diet quality score: HR,0.91 (95% CI, 0.62-1.31), plant-based diet indices: HR,1.10(95% CI, 0.75-1.62), empirical dietary index for hyperinsulinemia: HR,1.51 (95% CI, 1.00-2.29), empirical lifestyle Index for hyperinsulinemia: HR, 1.20 (95% CI, 0.83-1.73)
Zheng et al. 2021, U.S.[67]	Retrospective cross-sectional study	29,474 women (1,157 early-onset adenomas diagnosed before 50 years.)	Diet quality: western dietary pattern,	OR for high-risk adenoma for malignancy Western dietary pattern 5th (highest) (vs.1st lowest): OR, 1.67 (95% CI, 1.18-2.37), prudent dietary pattern 5th (highest) (vs.1st lowest): OR, 0.69 (95% CI, 0.48-0.98), Dietary Approaches-Stop Hypertension 5th (highest) (vs.1st lowest): 0.65 (95% CI, 0.45-0.93), Alternative Mediterranean Diet 5th (highest) (vs.1st lowest): 0.55 (95% CI, 0.38-0.79), Alternative Healthy Eating Index-2010 5th (highest) (vs.1st lowest): 0.71 (95% CI, 0.51-1.01) OR for low-risk adenoma for malignancy Western dietary pattern 5th (highest) (vs.1st lowest): OR, 1.25 (95% CI, 0.97-1.59), prudent dietary pattern 5th (highest) (vs.1st lowest): OR, 0.91 (95% CI, 0.71-1.17), Dietary Approaches-Stop Hypertension 5th (highest) (vs.1st lowest): OR, 1.01 (95% CI, 0.78-1.31), Alternative Mediterranean Diet 5th (highest) (vs.1st lowest): OR, 1.00 (95% CI, 0.77-1.29), Alternative Healthy Eating Index-2010 5th (highest) (vs.1st lowest): OR, 0.95 (95% CI, 0.74-1.23)

Abbreviations: AAPC, average annual percent change; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MMR, mismatch repair; OR, odds ratio; RR, relative risk; SD, standard deviation; SIR, standardized incidence ratio.

Supplementary Table 4. Summary of studies on risk factors for early-onset endometrial cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Haidopoulous et al. 2010, U.S.[68]	Case-control descriptive study	40 endometrial cancer patients (≤40 years) and 2 control groups: 1) 40 postmenopausal women previously diagnosed and treated with endometrial cancer; 2) 40 reproductive aged women (≤40 years) without endometrial cancer	age, height and weight, medical history, family history of malignancy in 1st degree relatives, parity and gravidity, use of oral contraceptives, age of menarche, menstruation characteristics, presenting symptom(s), smoking, history of hypertension	Early-onset endometrial cancer cases were more likely to be nulliparous (57.5% vs 17.5%; P=0.001), smokers (47.5% vs 5%; p<0.01), have history of irregular menstruation (45% vs 5%; P<0.001), have no history of hypertension (7.5% vs 55%; P<0.001), have family history of cancer (45% vs 17.5%; P=0.006) compared to later-onset cases. Early-onset endometrial cancer cases were more likely to be obese (BMI>30kg/m^2; 45% vs 20%; P=0.006), have history of irregular menstruation (45% vs 5%; P<0.001), have family history of cancer (45% vs 15%; P=0.003) compared to controls without endometrial cancer.
Raglan et al. 2019, multiple countries[69]	Meta-analysis		53 risk factors including anthropometric indices, dietary intake, physical activity, medical conditions, hormonal therapy use, biochemical markers, gynecological history, and smoking.	RR for early-onset endometrial cancer BMI (per 5 kg/m^2): RR, 1.49 (95% CI, 1.39-1.61)
Soliman et al. 2005, U.S.[70]	Case only descriptive study	188 endometrial cancer patients who were premenopausal and diagnosed at age <50 years stratified by age <40 years (n=79), age 41-45 years (n=49), age 46-49 years (n=60)	Clinical data, including age at diagnosis, presenting symptoms, race, BMI, gravidity, parity, menstrual history, oral contraceptive pill use, history of diabetes, hypertension, and personal and family history of cancer	Early-onset endometrial cancer cases were more likely to be obese (BMI>30kg/m^2), with greater prevalence in the subset of patients aged <40 years (62%) compared to cases age 46-49 years (56%) in stratified analysis. 54% were nulliparous overall, with higher prevalence in patients aged <40 years (71% were nulliparous).39% reported irregular menstruation with higher prevalence among patients aged <40 years (54% with irregular menstruation).
Walsh et al. 2008, U.K.[71]	Case only cross-sectional study	146 endometrial cancer patients age ≤50 years	Tumor immunostaining of mismatch repair proteins, personal history of cancer, family history of cancer	Among early-onset endometrial cancer patients, 18% were presumptive Lynch syndrome (defined as loss of at least one MMR gene protein by immunohistochemistry in their tumors, and, if there was immunohistochemical absence of *MLH1*, negative *MLH1* hypermethylation status). Those with presumptive Lynch syndrome were more likely to have a positive family history of any cancer (37.5% vs 1.3%; P=0.001).

Abbreviations: BMI, body mass index; CI, confidence interval; MMR, mismatch repair; RR, relative risk.

Supplementary Table 5. Summary of studies on risk factors for early-onset esophageal cancer (adenocarcinoma)

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Drahos et al. 2015, multiple countries[72]	Pooled 8 population-based case-control studies	1,363 esophageal adenocarcinoma cases, 1,472 esophagogastric junction adenocarcinoma cases, and 5,728 controls	BMI, cigarette smoking, alcohol consumption, recurrent gastroesophageal reflux variables (i.e., heartburn, regurgitation) and use of nonsteroidal anti-inflammatory drugs	Compared to controls, recurrent gastroesophageal reflux (OR, 8.06; 95% CI, 4.52-14.4), BMI ≥30 (vs <25 kg/m^2, 4.19; 95% CI, 2.23-7.87), and current smoking (vs. never smoking, OR, 2.72; 95% CI, 1.11-6.65) were associated with early-onset esophageal adenocarcinoma (age <50 years). Early-onset cancers had stronger associations with recurrent gastroesophageal reflux (p-value for effect modification = 0.01) and BMI (p-value for effect modification=0.04) compared to later-onset cases.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Supplementary Table 6. Summary of studies on risk factors for early-onset head and neck cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Toporcov 2015, multiple countries[73]	Pooled analysis of 25 case-control studies	2,010 cases and 4,042 controls with age ≤45 years; 17,700 cases and 22,704 controls with age >45 years	Smoking, alcohol consumption, diet, family history of cancer	<u>OR for head and neck cancer (<45 years), female</u> Ever smoking (vs. never): OR, 1.58 (95% CI, 1.22-2.06), pack-years (vs. never), >10 to 20 years: OR, 1.85 (95% CI, 1.26-2.72), >20 to 30 years: OR, 2.59 (95% CI, 1.60-4.18), >30 to 40 years: OR, 5.21 (95% CI, 1.75-9.90), >40 to 50 years: OR, 7.09 (95% CI, 2.89-17.3), and >50 years: OR, 6.50 (95% CI, 2.59-16.30), alcohol drinking (drinks/day x years) (vs. never), >50 to 60 years: OR, 4.21 (95% CI, 1.23-14.4), >60 years: OR, 2.78 (95% CI, 1.63-4.74), vegetable consumption 4th quartile (vs.1st quartile): OR, 0.67 (95% CI, 0.45-0.99), fruit consumption 4th quartile (vs.1st quartile): OR, 0.58 (95% CI, 0.38-0.88) <u>OR for head and neck cancer (<45 years), male</u> Ever smoking (vs. never): OR, 2.25 (95% CI, 1.86-2.71), pack-years (vs. never), >10 to 20 years: OR, 2.09 (95% CI, 1.65-2.66), >20 to 30 years: OR, 3.40 (95% CI, 2.66-4.35), >30 to 40 years: OR, 5.29 (95% CI, 3.85-7.26), >40 to 50 years: OR, 4.52 (95% CI, 3.11-6.56), and >50 years: OR, 5.41 (95% CI, 3.79-7.71), ever alcohol drinking (vs. never): OR, 1.32 (95% CI, 1.06-1.65), alcohol drinking (drinks/day x years) (vs. never), >60 years: OR, 2.31 (95% CI, 1.77-3.03), vegetable consumption (vs.1st quartile): 3rd quartile, OR, 0.60 (95% CI, 0.47-0.76), 4th quartile, OR, 0.58 (95% CI, 0.45-0.74), fruit consumption (vs.1st quartile): 2nd quartile, OR, 0.67 (95% CI, 0.53-0.84), 3rd quartile, OR, 0.70 (95% CI, 0.55-0.88), 4th quartile, OR, 0.57 (95% CI, 0.44-0.74). <u>OR for head and neck cancer (<45 years)</u> Family history of cancer in young relatives: OR, 2.27, (95% CI, 1.26, 4.10) <u>OR for oral cavity cancer (<45 years)</u> ever smoking (vs. never): OR, 1.91 (95% CI, 1.53-2.38) <u>OR for oropharynx cancer (<45 years)</u> ever smoking (vs. never): OR, 1.86 (95% CI, 1.47-2.37) and ever alcohol drinking (vs never): OR, 1.66 (95% CI, 1.25-2.21) <u>OR for larynx cancer: (<45 years)</u> ever smoking (vs. never): OR, 6.34 (95% CI, 3.98-10.1)

Abbreviations: CI, confidence interval; OR, odds ratio.

Supplementary Table 7. Summary of studies on risk factors for early-onset kidney cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Hemminki and Li 2004, Sweden[74]	Retrospective cross-sectional study.	1,516 sons and 899 daughters RCCs aged 0-68, and 11,137 fathers and 7394 mothers RCCs.	First degree relative	SIR for RCC (<50 years) Parental proband: SIR,1.87 (95% CI, 1.17-2.84), sibling proband: SIR, 4.78 (95% CI, 1.90-9.91)
Leiba et al. 2013, Israel[75]	Population-based cohort study	1,110,835 Jewish males 16-19 years (total 274 RCC cases) Renal cancer (mean age at RCC diagnosis is 44.0 ± 8.3 years)	BMI in adolescence (age 17)	HR for RCC BMI (vs. <22.5 kg/m^2): 22.5-24.9 kg/m^2, HR, 1.28 (95% CI, 0.96-1.73); 25.0-27.4 kg/m^2, HR, 1.16 (95% CI, 0.72-1.87), ≥27.5 kg/m^2, 2.43 (95% CI, 1.54-3.83)

Abbreviations: RCC, renal cell carcinoma; CI, confidence interval; HR, hazard ratio; SIR, standardized incidence ratio.

Supplementary Table 8. Summary of studies on risk factors for early-onset liver cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Lam et al. 2004, Hong Kong[76]	Cross-sectional study	121 HCC cases ≤40 years and 1,742 HCC cases > 40 years	Cirrhosis	Prevalence of cirrhosis: % Early-onset vs. later-onset: 1/98 (1%) vs.181/1435 (13%), P<0.0001
Liu et al. 2020, U.S.[77]	Case-control study (model development), prospective cohort study (validation)	173 at-risk population	Viral infection history of many viruses	AUC of viral exposure signature developed from case-control study: 0.91 (95% CI, 0.87-0.96) at baseline and 0.98 (95% CI, 0.97-1) at diagnosis in validation cohort.
Park et al. 2012, Korea[78]	Cross-sectional study	2,242 patients with HCC diagnosed before 45 years old (HBV (+) =223 vs. HBV (-) =62)	Family history	Family history (+) vs. (-): % (p value) Among 223 HBV (+) HCC: 191.1% vs.12.1 % (p=0.028). Among 62 HBV (-) HCC: 17.2% % vs.11.4 % (p=0.244)
Wan et al. 2011, U.S.[79]	Cross-sectional study	168 cases of HCC in Asians with HBV (74% (124/168) ≥ 50 years vs. 199 HBV control and 26% (44/168) <50 years vs. 432 HBV control)	Sex, family history of HCC, history of smoking, (Early-onset HCC <40 for male and <50 for female)	OR for early-onset HCC Male (vs. female): OR, 2.7 (95% CI 1.0-7.0), Family history: OR, 2.7 (95% CI, 1.0-7.0), smoking history: OR, 3.4 (95% CI, 1.5-8.0)
Yang et al. 2002, Taiwan[80]	Prospective cohort study	11,893 men (2,361 with HBsAg and 370 with both HBeAg and HBsAg), HCC cases diagnosed ≤ 55 years	Hepatitis B antigen	RR for HCC Positive only for HBsAg: RR, 6.1 (95% CI, 3.3-11.4), positive both for HBsAg and HBeAg (vs. negative for both): RR, 25.4 (95% CI, 13.3-48.6)

Abbreviations: AUC, area under the receiver operating characteristics curve; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma. OR, odds ratio; RR, relative risk.

Supplementary Table 9. Summary of relevant studies on early-life risk factors for multiple myeloma

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Birmann et al. 2017, multiple countries[81]	Pooled analysis of eight case-control studies	2,318 myeloma cases and 9,609 controls	Adult BMI, young adult BMI (age 25 or 30 years)	OR for overall multiple myeloma Adult BMI (per 5 kg/m^2): OR, 1.09 (1.04-1.14), young adult BMI (per 5 kg/m^2): OR, 1.2 (1.1-1.3)
Marinac et al. 2018, U.S.[82]	Prospective cohort study	49,374 men and 153,260 women (575 cases)	Cumulative average BMI, young adult BMI, BMI change (from young adulthood), physical activity	HR for overall multiple myeloma Cumulative average BMI (per 5 kg/m^2): HR, 1.20 (1.06-1.37) Young adult BMI (per 5 kg/m^2): HR, 1.30 (1.13-1.50) BMI change, physical activity: not significant HR for overall multiple myeloma, male Cumulative average BMI (per 5 kg/m^2): HR, 1.33 (1.09-1.63) Young adult BMI (per 5 kg/m^2): HR, 1.42 (1.16-1.73) BMI change, physical activity: not significant For women, there was not significant results.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

Supplementary Table 10. Summary of studies on risk factors for early-onset pancreatic cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Juo et al. 2018, U.S.[83]	Cross-sectional study	28,053 of pancreatic cancers across all ages (non-obese: 26,834, obese: 942, morbidly obese: 277) vs. 1,743 pancreatic cancers diagnosed < 50 years (non-obese: 1,632, obese: 79, morbidly obese: 32)	Obesity (BMI > 30), morbid obesity (BMI > 40), smoking, alcoholism	Association between obesity and onset age for entire sample Obesity (vs. non-obese): -5.35 (± 0.72), P<0.05, morbid obesity (vs. nonobese): -8.19 (± 1.25), P<0.05
McWilliams et al. 2016, multiple countries[84]	Case-control study	1,954 pancreatic cancer cases <60 years (vs. 3,278 control) 226 pancreatic cancer cases <45 years (vs. 589 control)	Alcohol, family history, smoking	OR for pancreatic cancer (<60 years) Alcohol ≥26 g/day (vs. <26 g/day): OR, 1.49 (95% CI, 1.21-1.84), smoking, 1-19 packs/year, 20-39 packs/year, and ≥40 packs/year (vs. no smoking): OR, 1.40 (95% CI, 1.18-1.65), OR, 2.29 (95% CI, 1.89-2.76), and OR, 2.79 (95% CI, 2.24-3.48) OR for early-onset pancreatic cancer (<45 years) Alcohol ≥26 g/day (vs. <26 g/day): OR, 2.18 (95% CI, 1.17-4.09), family history (vs. no): OR, 2.88 (95% CI, 1.04-7.99), smoking, 1-19 packs/year, 20-39 packs/year, and ≥40 packs/year (vs. no smoking): OR, 1.39 (95% CI, 0.90-2.16), OR, 1.87 (95% CI, 1.08-3.23), and OR, 2.23 (95% CI, 0.91-5.47)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Supplementary Table 11. Summary of studies on risk factors for early-onset prostate cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Al-Jebari et al. 2019, Sweden[85]	Prospective cohort study	1,181,490 fathers (in vitro fertilization, N=20,618, intra-cytoplasmic sperm injection, N=14,882 vs. natural conception, N=1,145,990)	Infertility treatment by assisted reproduction	Among men who became fathers, treatment by assisted reproduction was significantly associated with increased prostate cancer risk diagnosed before the age of 55 years. HR for prostate cancer risk (<55 years) (vs. natural conception) Intra-cytoplasmic sperm injection: HR, 1.86 (95% CI, 1.25-2.77), in vitro fertilization: HR, 1.51 (95% CI, 1.09-2.08)
Brandt et al. 2010, Sweden[86]	Prospective cohort study	>11.8 million individuals including 2,229 prostate cancer patients diagnosed at <55 years, of whom 590 were familial.	Number and the diagnosis age of affected first-degree relatives	HR for prostate cancer increased with the number of affected relatives. HR for prostate cancer (<55 years) (affected first-degree relatives vs. non-affected first-degree relatives) Father only: HR, 2.93 (95% CI, 2.64-3.25), brother only: HR, 4.41 (95% CI, 3.59-5.42), father and one brother: HR, 11.32 (8.47-15.13), two brothers: HR, 5.90 (95% CI, 2.45-14.20), father and two brothers: HR, 8.06 (95% CI, 2.02-32.27), three brothers: HR, 23.26 (5.81-93.1).
Lange et al. 2012, U.S.[87]	Cross-sectional study	754 unrelated Caucasian American with prostate cancer diagnosed at age ≤ 55 years and 2,713 controls	Genetic factors (14 SNPs)	13 of 14 SNPs were associated with early-onset prostate cancer. Early-onset prostate cancer diagnosed at age < 50 years had significantly more risk alleles (mean number of risk alleles=12.8) compared to those diagnosed at age 50-55 years (mean number of risk alleles=12.1; P=0.0003).

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative risk; SIR, standardized incidence ratio; SNP, single nucleotide polymorphism.

Supplementary Table 12. Summary of studies on risk factors for early-onset stomach cancer

Study, country	Study design	Participants	Exposures	Results (RR, HR, OR, or descriptive statistics)
Bacani JT et al. 2006, Canada[88]	Descriptive study	211 early-onset gastric cancer cases	*CDH1* germline mutations	The overall frequency of germline *CDH1* mutations was 1.3% (1 case among 81 cases) for early-onset gastric cancer and 2.8% (1 case among 36 cases) for early-onset isolated cell gastric cancer.
Bergquist et al. 2019, U.S.[89]	Ecological study at county-level	75,225 gastric cancer patients (20-59 years: 18,608 vs 60 years and older: 56,617)	Smoking, binge drinking	20-59 years vs. ≥60 years: R^2 Smoking R^2= 0.02989, p= 0.08964 vs. R^2=-0.01444, P=0.7664, Binge drinking R^2= 0.05726, P=0 .0307 vs. R^2=-0.01584, P=0.9633
De et al. 2018, U.S.[90]	Cross-sectional study	2615 patients under 40 years and 67,479 patients with age 40 years or older who had gastric adenocarcinoma	Sex, race/ethnicity	Compared to older patients, adults under 40 years are more likely to be female (46% vs. 35%), more likely to be Hispanic (32% vs. 11%) and less likely to be White (69% vs. 76%).
Giryes et al. 2018, U.S.[91]	Ecological study at state-level	95,323 gastric cancer patients (early-onset aged 20-39 years: 3,247 vs. traditional-onset aged 40 years and older: 92,076)	Smoking, heavy alcohol drinking	20-39 years vs. ≥40 years: R^2 Current smoking: 0.089 (P=0.794) vs.0.221 (P=0.513), heavy alcohol drinking: 0.661 (P=0.027) vs.0.751 (P=0.008)
Gronberg et al. 2000, Sweden[92]	Descriptive analysis	1,364 first-degree relatives of the men with prostate carcinoma in 62 families with hereditary prostate carcinoma	Hereditary prostate carcinoma in the first-degree relatives	SIR for gastric carcinoma ≤65 years: SIR 3.39 (1.24-7.37) vs. >65 years: SIR 2.51 (1.20-4.62)
Juo et al. 2018, U.S.[93]	Cross-sectional study	20,401 of gastric cancer across all ages (non-obese: 19,416, obese: 760, morbidly obese: 225) Among them, 2,321 of gastric cancer diagnosed at <50 (non-obese: 2,197, obese: 88, morbidly obese: 36)	Obesity (BMI >30), morbid obesity (BMI >40)	Reduction in cancer diagnosis age (years) Obesity (vs. nonobese): - 3.25 (± 0.53), P<0.05, morbid obesity (vs. nonobese): - 5.48 (± 0.96), P<0.05
Kwak et al. 2015, Korea[94]	Cross-sectional study	4,282 patients diagnosed with gastric cancer (924 patients with vs. 3,358 patients without first degree family history of gastric cancer)	Family history	Age at diagnosis of patient with first-degree family member diagnosed with gastric cancer before 50 years old vs. after 50 years old Father: 47.7 ± 10.3 years vs. 55.3 ± 10.1 years (P< 0.001), Mother: 48.6 ± 10.4 years vs. 58.2 ± 9.5 years (P< 0.001), Sibling: 57.4 ± 11.5 years vs.64.3 ± 8.1 years (P< 0.001)

Rugge et al, 1999, Italy[95]	Case-control study	105 gastric carcinoma patients (mean age: 34.4 years, range: 16-40 years) and an equal number of age- and sex-matched controls	*H. pylori* infection	OR (95% CI) for gastric cancer H. Pylori infection (vs. no infection): 2.79 (1.52-5.11)
Zhou F et al. 2016, China[96]	Cross-sectional study	152 young patients (≤40 years) and 250 old patients (>40 years)	Sex, family history	Compared to old gastric cancers, the young gastric cancer cohort was more predominant in women and showed more positive family history of gastric cancer.

Abbreviations: CI, confidence interval; BMI, body mass index; OR, odds ratio; SIR, standardized incidence ratio.

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