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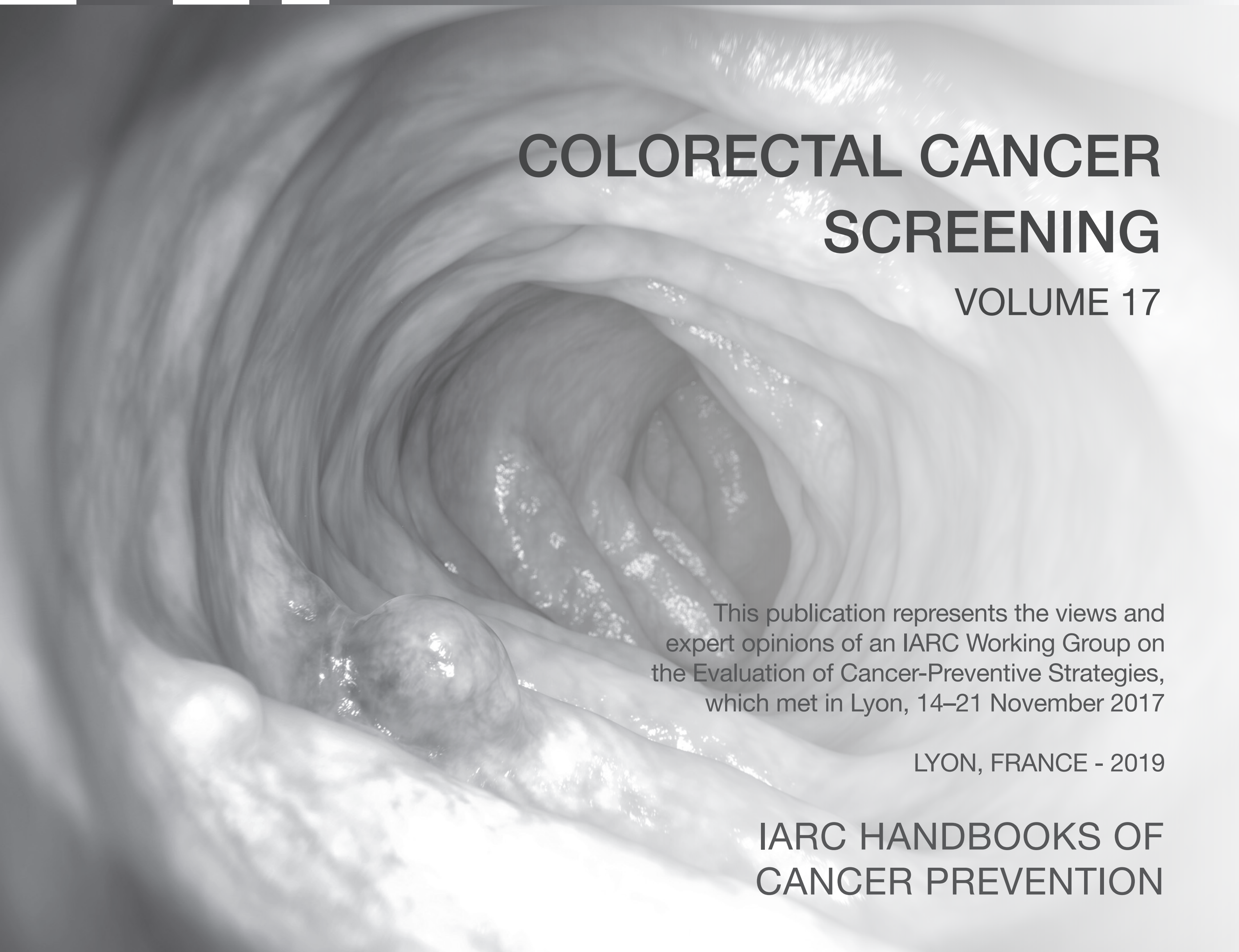

COLORECTAL CANCER SCREENING

VOLUME 17

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IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

1. COLORECTAL CANCER

1.1 Global burden: incidence, mortality, survival, and projections

1.1.1 Global burden

Colorectal cancer (CRC), or cancer of the large bowel, is defined here as an aggregate term covering cancers of the colon (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code, C18), the rectosigmoid junction (ICD-10 code, C19), and the rectum (ICD-10 code, C20). Although there are exceptions, cancers of the colon usually constitute the largest subgroup and can make up two thirds of the total, with cancers of the rectosigmoid junction and the rectum making up one third.

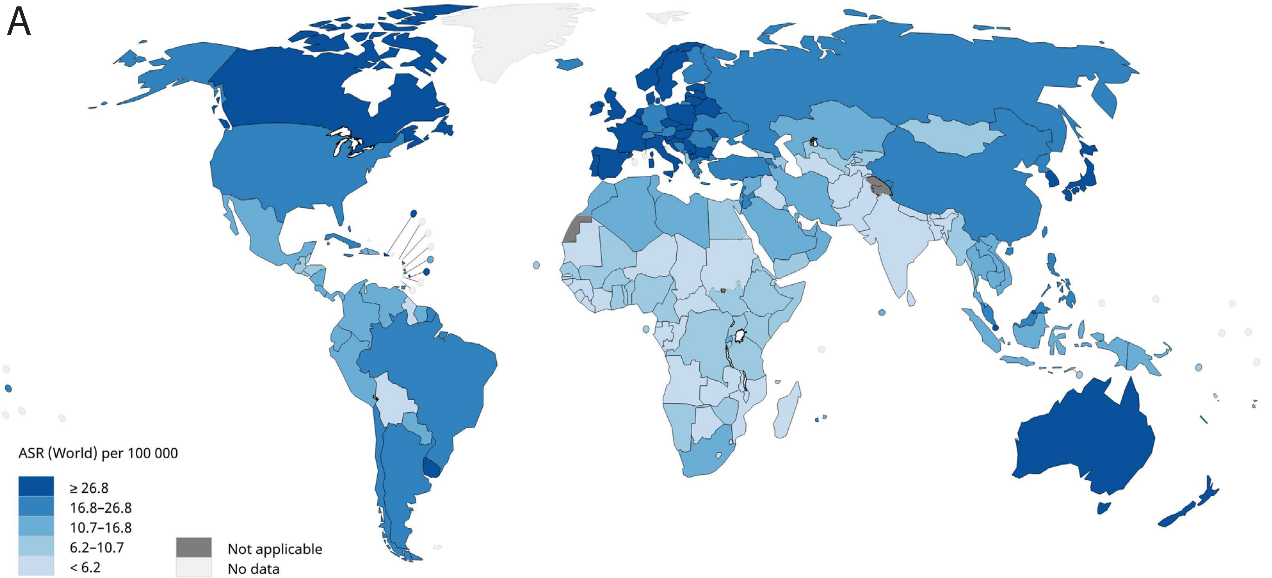
CRC is the third most common cancer in men and the second most common cancer in women worldwide. According to the most recent estimates from GLOBOCAN (Ferlay et al., 2018a), in 2018 there were an estimated 1 006 000 new cases in men and 795 000 in women. CRC represented more than 10% of the global cancer burden; the proportions were higher only for cancers of the lung and prostate (in men) and cancer of the breast (in women). In 2018, the global age-standardized incidence rate (ASIR) for CRC was 23.1 per 100 000 in men and 15.7 per 100 000 in women. In 2018, there were an estimated 475 000 deaths from CRC in men and 387 000 in women, and the age-standardized mortality rate (ASMR) was 10.6 per 100 000 in men and 7.0 per 100 000 in women. There were an estimated 2.5 million men and 2.1 million women alive at the end of 2018 who had been diagnosed with CRC in the preceding 5 years. These 4.6 million cancer survivors represent about 12% of all 5-year cancer survivors (Ferlay et al., 2018a).

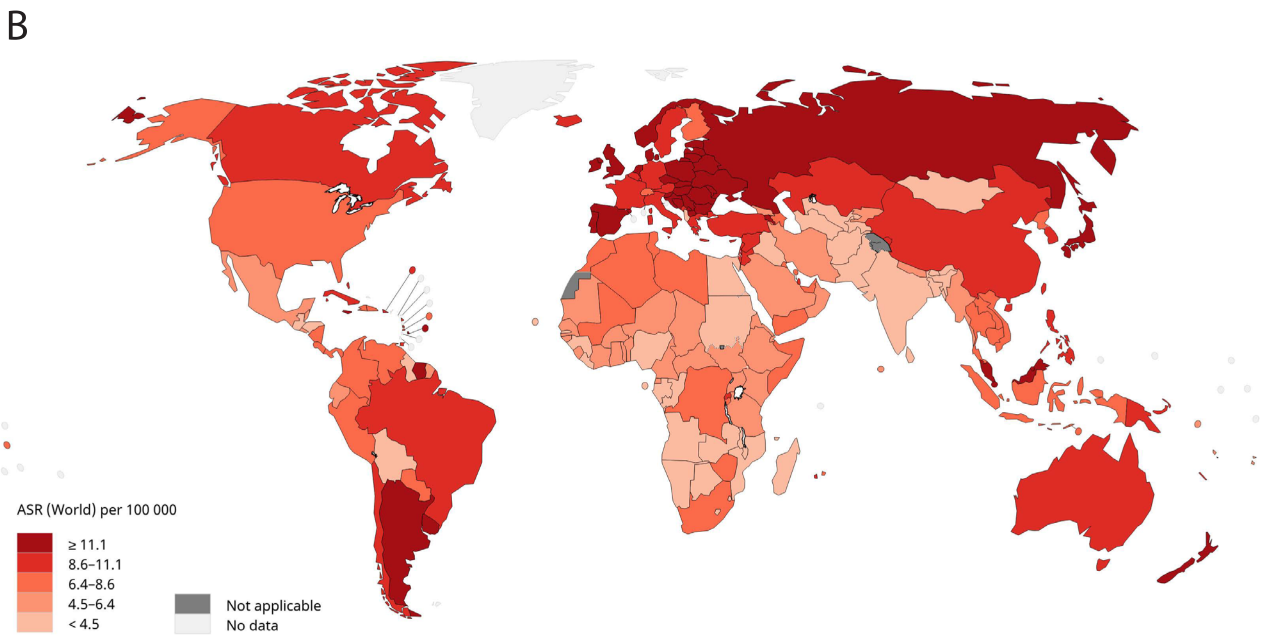
Like for most types of cancer, incidence and mortality rates of CRC increase markedly with age, and most cases and deaths occur in people older than 50 years. Of the worldwide burden of 1.80 million incident cases in 2018, 0.18 million (10%) were estimated to occur in people younger than 50 years, 1.07 million (59%) in those aged 50–74 years, and 0.55 million (31%) in those aged 75 years and older (Ferlay et al., 2018a).

1.1.2 International variation and relationship with socioeconomic development

CRC incidence rates vary substantially across the world, with the highest rates observed in Australia and New Zealand, Europe, East Asia, and North America. Incidence rates vary 10-fold in both sexes, and the estimated incidence rates are highest in Australia and New Zealand (ASIR, 40.6 and 30.5 per 100 000 in men and women, respectively) and lowest in South-Central Asia (ASIR, 5.6 and 3.5 per 100 000 in men and women, respectively) (Fig. 1.1 and Fig. 1.2). CRC mortality rates also vary across the world (although less so than those for incidence), up to 5-fold in both men and women. In both sexes, the estimated mortality rates are highest in central and eastern Europe (ASMR, 20.3 and 11.7 per 100 000 in men and women, respectively) and

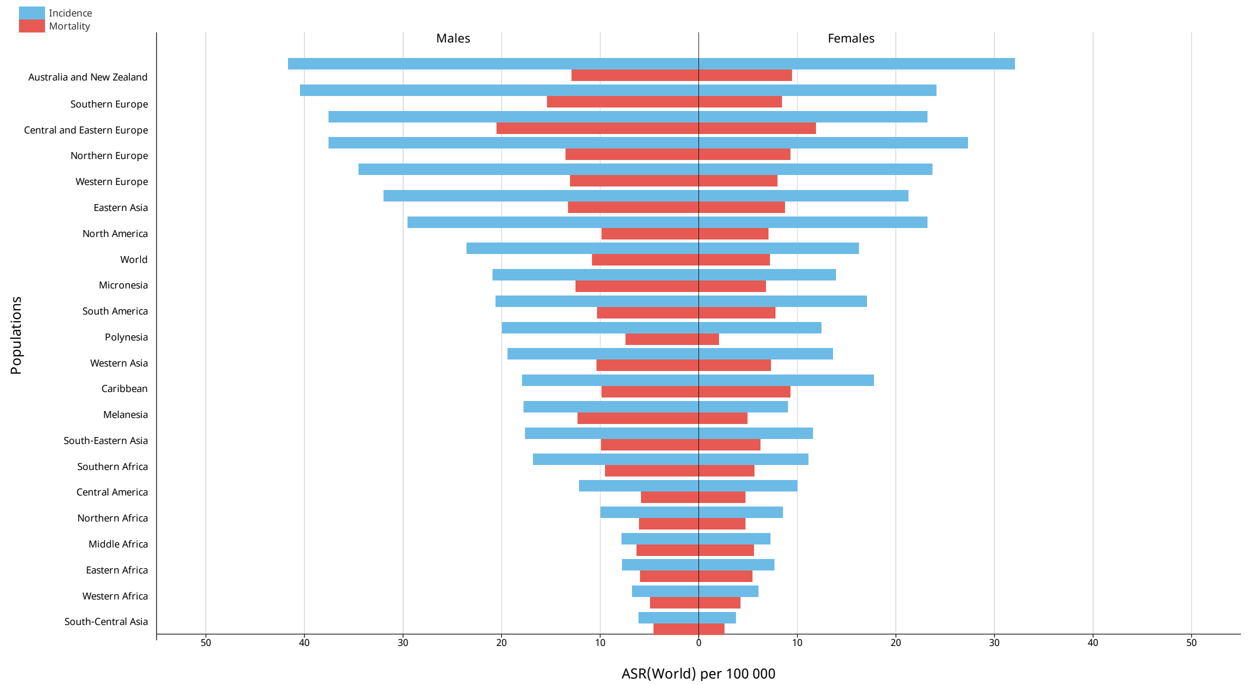
Fig. 1.1 Global distribution of estimated age-standardized (World) incidence (A) and mortality (B) rates per 100 000 for colorectal cancer in men and women, 2018





From GLOBOCAN 2018 (Ferlay et al., 2018a).

Fig. 1.2 Estimated age-standardized incidence and mortality rates per 100 000 for colorectal cancer in men and women, by large world regions, 2018



From GLOBOCAN 2018 (Ferlay et al., 2018a).

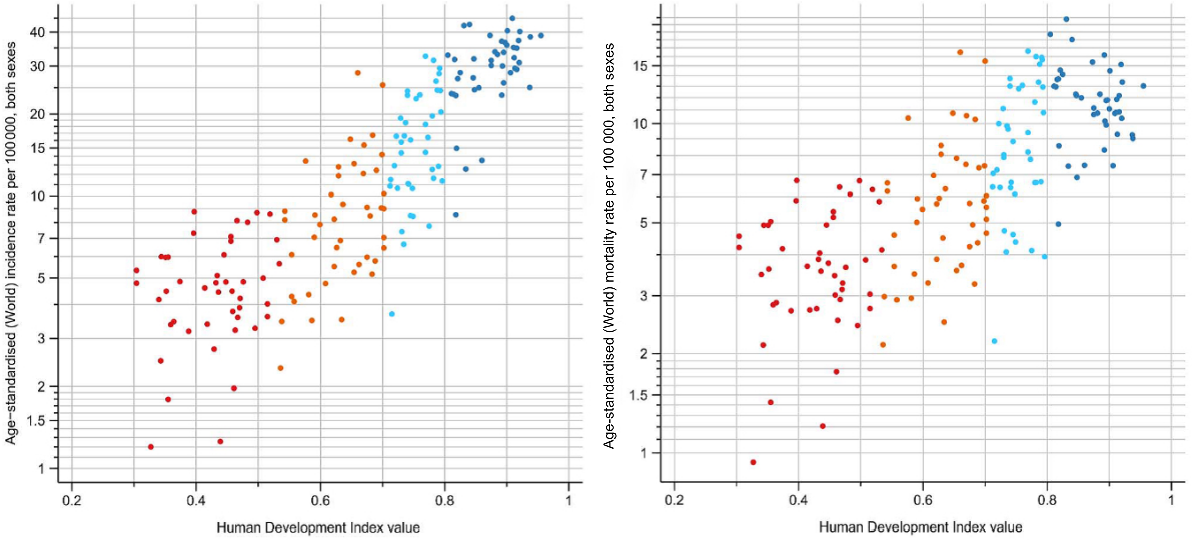
lowest in South-Central Asia in men (ASMR, 4.3 per 100 000) and in Polynesia in women (ASMR, 2.1 per 100 000) (Fig. 1.1 and Fig. 1.2).

In general, CRC incidence rates show a strong positive gradient with the level of economic development, and the highest rates are observed in countries with very high levels of the Human Development Index (HDI) (Fig. 1.3) (Arnold et al., 2017). The incidence rate of CRC is considered to be one of the clearest indicators of disease transition in societies undergoing socioeconomic development and transition to a lifestyle more typical of industrialized countries (Fidler et al., 2017).

1.1.3 Survival

The regions of the world with the highest CRC incidence rates tend to have relatively low CRC mortality rates compared with parts of Africa, Asia, and South America where incidence rates are lower but, because of lower rates of survival, mortality-to-incidence ratios are considerably higher (Fig. 1.2). According to the CONCORD-3 study, the 5-year net survival for patients diagnosed in 2010–2014 was between 60% and 70% in most countries in North America and western Europe and less than 50% in several countries in Africa, Asia, eastern Europe, and South America, in some of which it was less than 40% (Allemani et al., 2018).

Fig. 1.3 Correlation between age-standardized (World) colorectal cancer incidence rates (left panel) and mortality rates (right panel) and Human Development Index (HDI) in both sexes combined



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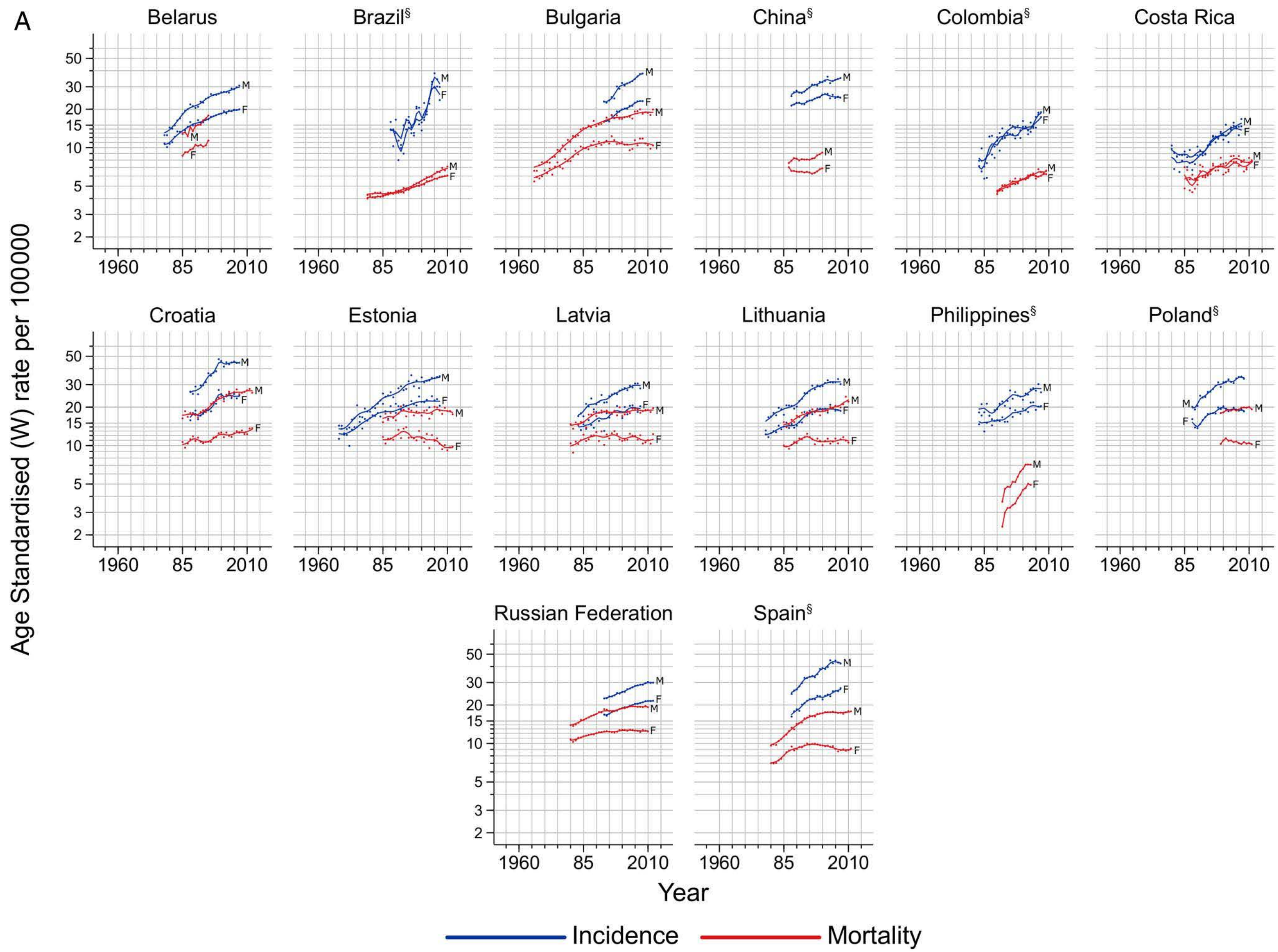
1.1.4 Time trends

An analysis of CRC incidence and mortality trends over time revealed three distinct patterns by country (or population): increasing or stable incidence and mortality rates (group A), increasing incidence rates and decreasing mortality rates (group B), and decreasing incidence and mortality rates (group C) (Fig. 1.4) (Arnold et al., 2017). Group A comprised several populations in Asia, eastern Europe, and South America, whereas groups B and C comprised populations in Australia and New Zealand, Europe, Israel, Japan, North America, and Singapore. The increasing CRC mortality rates observed in group A presumably reflect increasing background incidence in populations where health service resources have not been adequate – to detect the disease at early stages and/or manage the disease once detected – to positively affect population mortality. In contrast, the decreasing CRC mortality rates observed in groups B and C are likely to represent the effects of efforts to improve early diagnosis, including through screening programmes in some countries, allied with improving treatment and management practices. The extent to which screening programmes may also act to decrease incidence rates, through detection and removal of precancerous polyps, is difficult to determine. However, this may partly explain the CRC incidence trends observed in some of the countries in group C, in some of which (e.g. Israel, Japan, and the USA) opportunistic screening has been in place for several decades. In the USA, microsimulation modelling has suggested that the decline in CRC mortality rates is consistent with a relatively large contribution from screening and a smaller but demonstrable impact of reduction in exposure to risk factors and improvements

Fig. 1.4 Trends in colorectal cancer incidence and mortality rates in men (M) and women (F) for selected countries



§ Regional data. Group A, increasing or stable incidence and mortality rates. Group B, increasing incidence rates and decreasing mortality rates. Group C, decreasing incidence and mortality rates.

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Fig. 1.4 (continued)

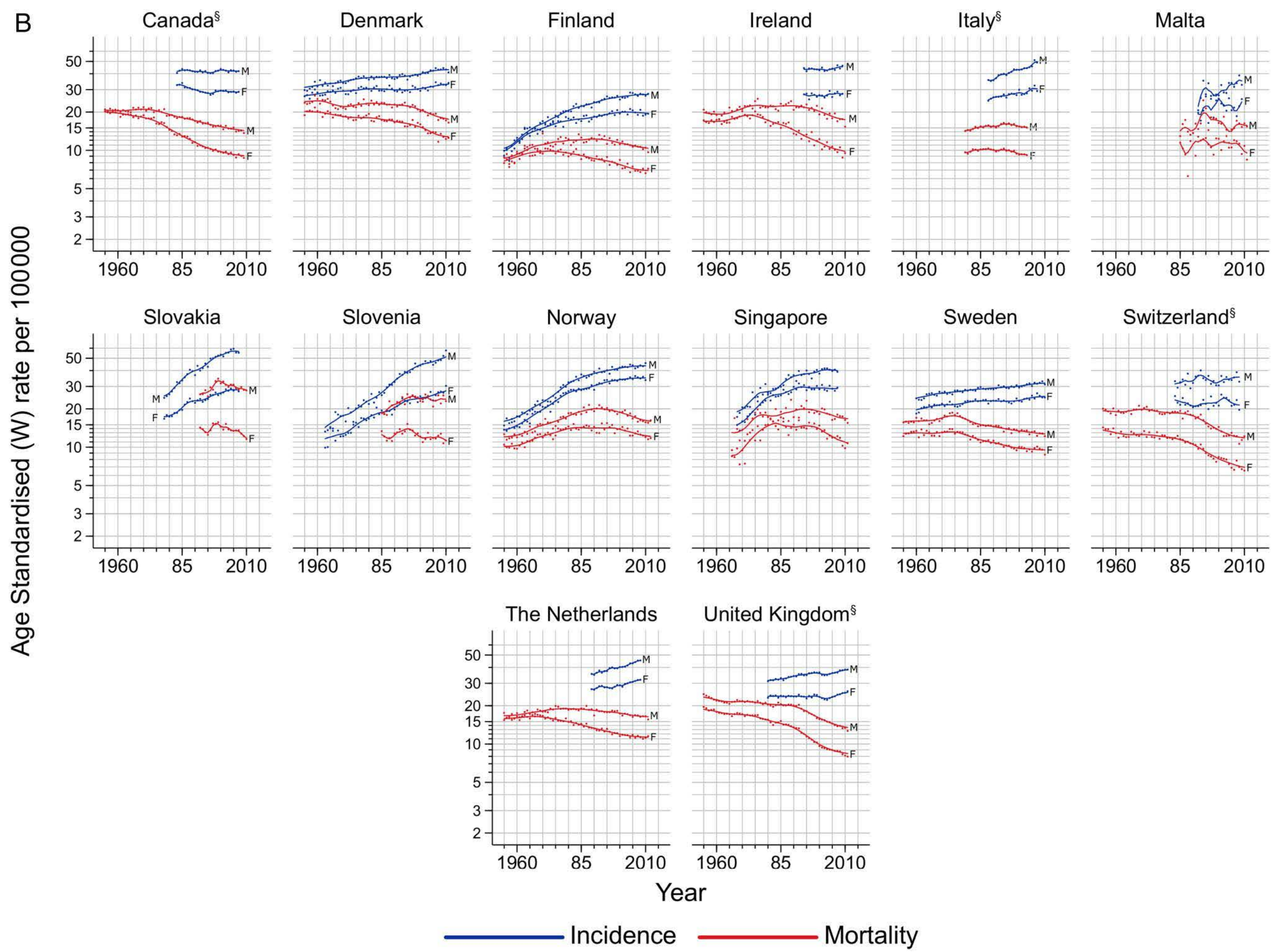


Fig. 1.4 (continued)

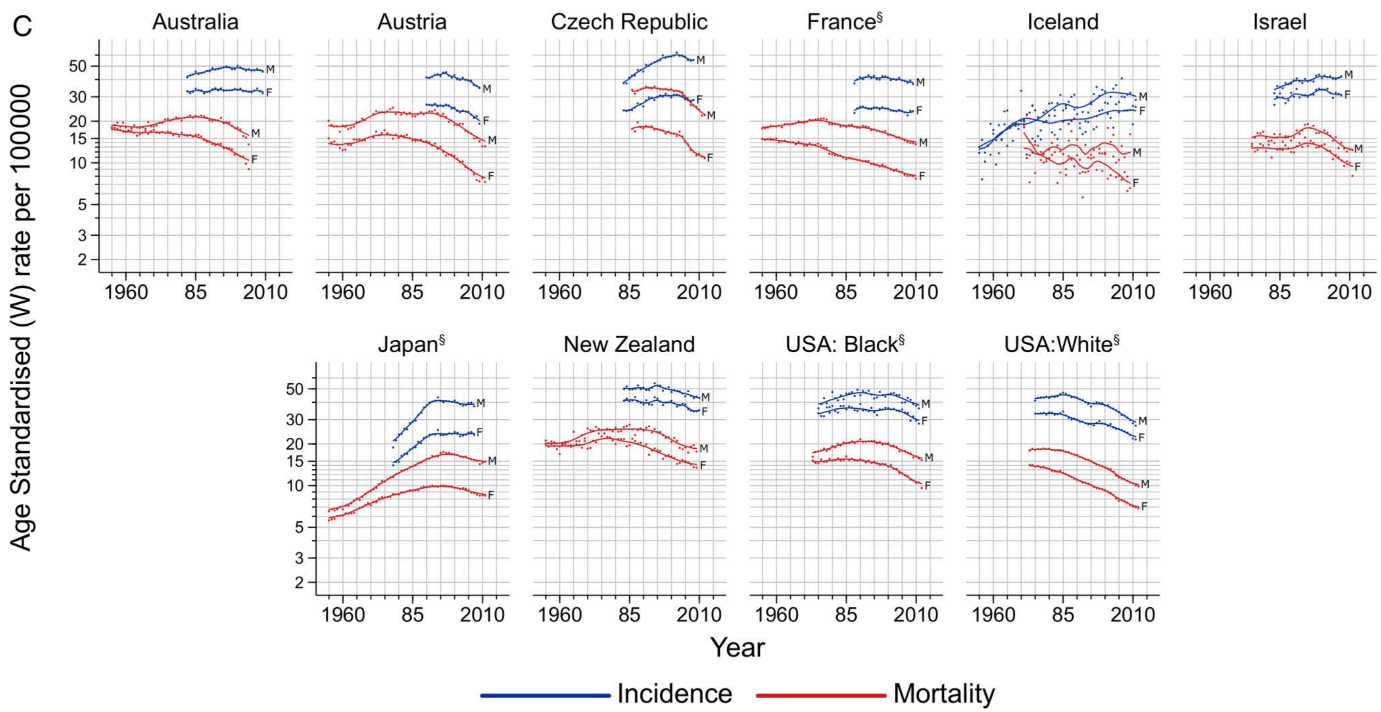
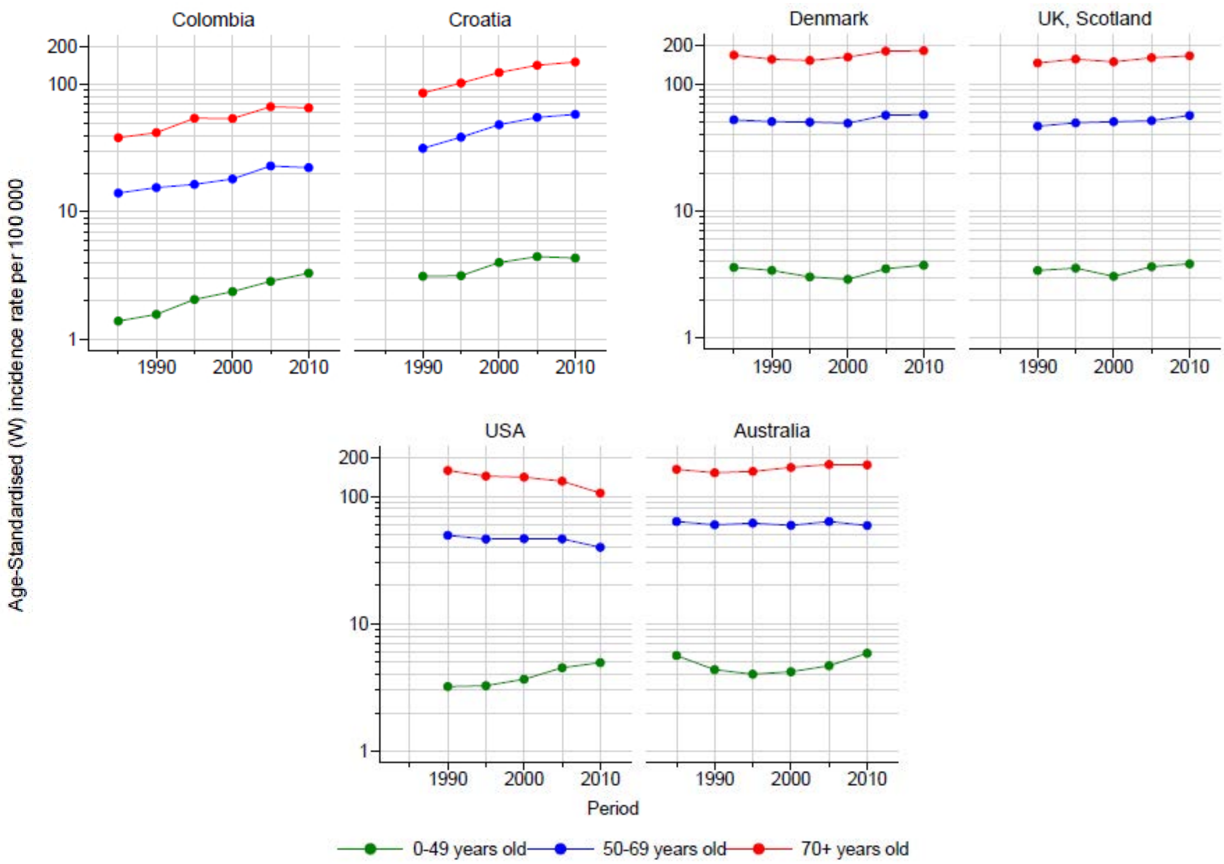


Fig. 1.5 Trends in colorectal cancer incidence rates by age group (0–49, 50–69, and ≥ 70 years) in both sexes combined for selected countries



Compiled from Ferlay et al. (2018b). Each data point corresponds to the middle of the 5-year period of a volume (e.g. 1985 for 1983–1987 for Volume VI). Data are provided by national cancer registries for Croatia, Denmark, and Scotland, United Kingdom and regional cancer registries for Australia (New South Wales, Tasmania, Victoria, and Western Australia), Colombia (Cali), and the USA (SEER 9 registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle–Puget Sound, and Utah). Colorectal cancer is defined as colon (ICD-10 code, C18) and rectum (ICD-10 code, C19–20).

in treatments (Edwards et al., 2010). Changes in exposure profiles and/or screening modalities would probably explain all of the decrease in incidence rates in countries, such as New Zealand, where organized screening has only been introduced relatively recently (and is likely to cause an initial increase in detection of prevalent cases) (Schreuders et al., 2015; Arnold et al., 2017) (see Section 2 for screening practices).

Fig. 1.5 shows time trends in CRC incidence rates by broad age groups (0–49, 50–69, and ≥ 70 years) for selected countries. Although incidence rates have been either increasing or stable over time in all three age groups in most of the countries shown, this is not the case for the USA, where rates have decreased in the two older age groups but have increased in those younger than 50 years (especially in the most recent time period). As stated above, opportunistic screening practices in the USA are likely to have contributed to the observed decreases in the older age groups. Recent increases in CRC incidence rates among people younger than 50 years have been reported in Australia, Canada, and the USA (Patel & De,

Table 1.1 The global burden of colorectal cancer: estimated annual numbers of incident cases and deaths, by HDI ranking and for the world, in 2018 and projected to 2040

2015 level of HDI[a]	Population (millions)[b]	Number of cases (millions)[c]			Number of deaths (millions)[c]		
	2015	2018	2040[d]	Increase (%)	2018	2040[d]	Increase (%)
Very high	1388	0.88	1.20	36	0.38	0.56	47
High	2459	0.73	1.27	74	0.36	0.70	94
Medium	2759	0.17	0.30	76	0.11	0.20	81
Low	1022	0.03	0.07	119	0.02	0.05	121
World	7628	1.80	3.08	71	0.86	1.56	81

HDI, Human Development Index.
[a] The HDI is a composite index based on life expectancy at birth, expected and mean years of schooling, and gross national income per capita (expressed in purchasing power parity dollars). Predefined categories of the distribution of HDI by country have been used: low (HDI < 0.55), medium (0.55 ≤ HDI < 0.7), high (0.7 ≤ HDI < 0.8), and very high (HDI ≥ 0.8) (UNDP, 2017).
[b] Derived from UNDP (2017).
[c] Derived from GLOBOCAN 2018 (Ferlay et al., 2018a).
[d] The 2040 projection is based on demographic change and constant risk.

2016; Siegel et al., 2017; Troeung at al., 2017). These increases, which occurred after a period of declining incidence, may be due to changes in exposure to risk factors in the age group younger than 50 years (notably the increased prevalence of obesity) and/or earlier detection of existing cancers.

1.1.5 Projections of global burden

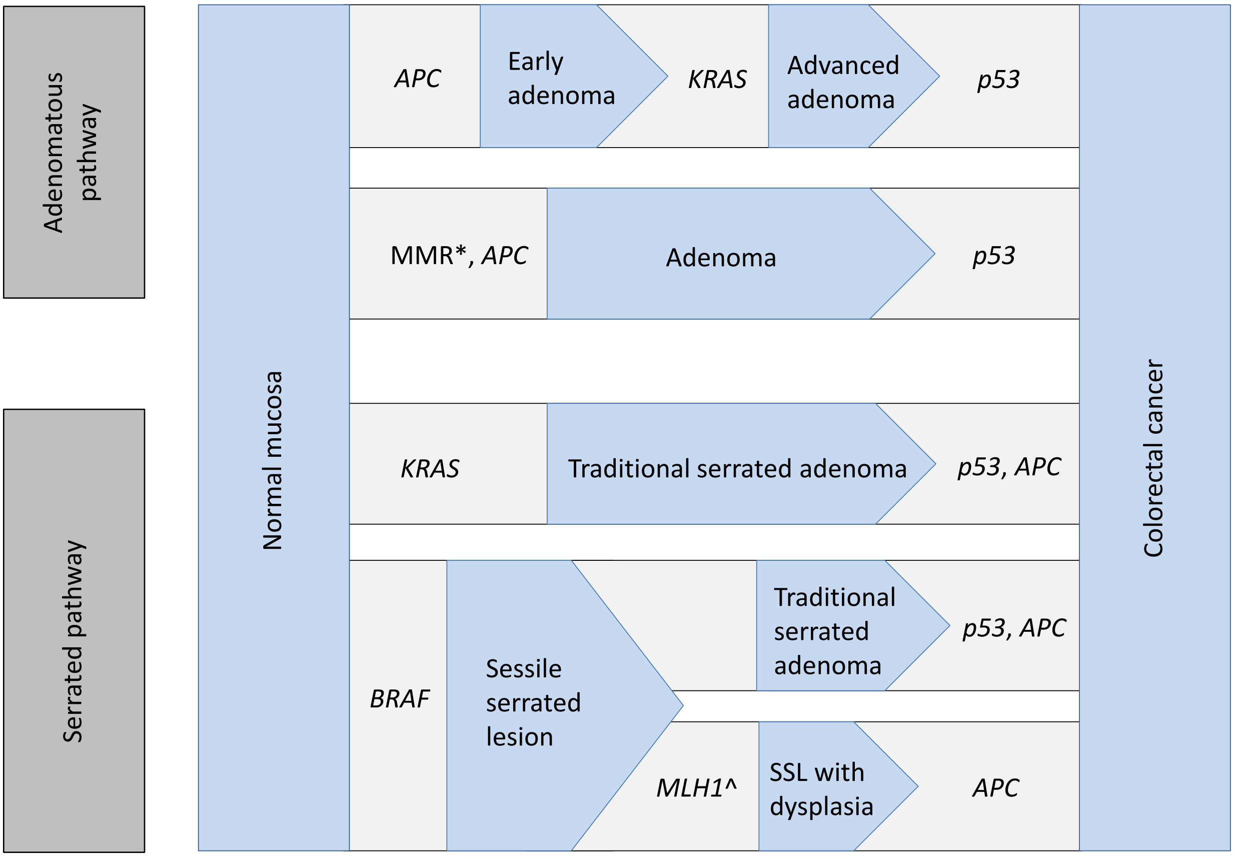
Table 1.1 shows the estimated global burden of CRC incidence and mortality in 2018 and projected to 2040, overall and by HDI category. Overall, a 71% increase in the estimated number of new cases (from 1.80 million to 3.08 million) and an 81% increase in the number of deaths (from 0.86 million to 1.56 million) are projected by 2040. Because of differential population growth levels among different HDI categories, the numbers of new cases and deaths are projected to increase more rapidly in countries with lower HDI. Although the number of new cases will remain highest in countries with very high HDI, by 2040 the number of deaths will be highest in countries with low HDI.

It is important to note that these projections take into account only global demographic changes in population structure and growth based on United Nations estimates (UNDP, 2017). The risk of developing or of dying from CRC is assumed to remain constant at 2018 levels, and no allowance is made for changes in increased detection or improvements in survival.

1.2 Classification and natural history

Several guidelines for the classification of colorectal diseases are available, as well as diagnostic criteria for relevant lesions in the population screening programmes for CRC (Quirke et al., 2011, 2012; Vieth et al., 2011; WHO Classification of Tumours Editorial Board, 2019). This section highlights the most important premalignant lesions, their risk of disease progression, and the different CRC subtypes. It also briefly touches upon the molecular background of colorectal tumours (summarized in Fig. 1.6), which is described more extensively in Müller et al. (2016), Dienstmann et al. (2017), and Rodriguez-Salas et al. (2017) (see also Section 3.8).

Fig. 1.6 Simplified diagram of colorectal cancer pathways



SSL, sessile serrated lesion.
This figure indicates the molecular pathways to colorectal cancer, but there is no clear correlation with the different histological subtypes. The indicated genes are mutated either before carcinogenesis (*APC* in familial adenomatous polyposis and the mismatch repair genes [MMR*] in Lynch syndrome) or during carcinogenesis (in sporadic colorectal cancer); *MLH1^* indicates hypermethylation.
Compiled by the Working Group using data from Bettington et al. (2015, 2017) and Fearon & Vogelstein (1990).

1.2.1 Classical adenomas

Classical adenoma is the best-known precursor of CRC. By definition, this is a lesion that contains unequivocal epithelial neoplasia. The majority of these lesions develop after a mutation occurs in the *APC* gene (Fearon & Vogelstein, 1990). According to the World Health Organization (WHO) guidelines (Bosman et al., 2010), three morphological types can be distinguished according to the percentage of "villousness": tubular adenoma (< 25% villous), tubulovillous adenoma (25–75% villous), and villous adenoma (> 75% villous). These subtypes can be further divided according to the grade of neoplasia. Although initially a three-tiered system was proposed (low-, intermediate-, and high-grade neoplasia), for the sake of reproducibility, this has been discarded and a universally accepted two-tiered system (low- and high-grade neoplasia) is used. This distinction between low- and high-grade neoplasia should be made on the basis of histological criteria; architectural changes that are indicative of high-grade neoplasia (marked complex glandular crowding and irregularity of glands, cribriform architecture, and intraluminal necrosis) should be accompanied by significant loss of cell polarity, markedly enlarged nuclei with prominent nucleoli, and dispersed chromatin pattern, often with atypical mitotic figures. The percentage of cases with high-grade neoplasia is used as a quality indicator for pathology, and it varies from less than 5% in programmes using colonoscopy to less than 10% in programmes using stool-based tests for blood (Quirke et al., 2011).

A special subcategory, advanced adenoma, has been defined for evaluation in population screening programmes. Advanced adenomas are those adenomas with a size of more than 10 mm and/or with tubulovillous or villous architecture and/or with high-grade neoplasia. Depending on national guidelines, these features may be important for the determination of the subsequent surveillance intervals.

The presence of advanced adenomas compared with non-advanced adenomas is associated with an increased risk of developing subsequent adenomas or CRC (Atkin et al., 1992; Cottet et al., 2012). Whereas the 10-year cumulative risk of developing CRC was reported to be 2.3% for patients with classical adenoma (Erichsen et al., 2016), it was estimated to be as high as 40% for elderly patients with advanced adenoma, from large-scale population studies in Germany (Brenner et al., 2007).

1.2.2 Serrated lesions and polyps

Serrated lesions and polyps are characterized by a serrated (sawtooth or stellate) architecture of the epithelium. Serrated lesions and polyps form a spectrum of lesions that have only relatively recently been found to be related to the development of CRC. As per current terminology (WHO Classification of Tumours Editorial Board, 2019), there are three types of serrated lesions and polyps: hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas.

The most common type of serrated polyp is the hyperplastic polyp. Hyperplastic polyps are often small lesions (< 5 mm in diameter) and are frequently found in the distal colon. Diminutive and distal hyperplastic polyps have no significant malignant potential and do not affect colonoscopic surveillance intervals; however, proximal microvesicular hyperplastic polyps are likely to be a precursor of sessile serrated lesions (WHO Classification of Tumours Editorial Board, 2019).

Sessile serrated lesions ("sessile serrated adenomas" and "sessile serrated polyps" are not recommended nomenclature) are considered to be precursor lesions of CRC. These lesions share with hyperplastic polyps the serrated crypt structures, but architectural distortion is also present: horizontal growth along the muscularis mucosae, dilation of the crypt base (basal third of the crypt), serrations extending into the crypt base (in contrast to superficial serrations in hyperplastic polyps), and asymmetric proliferation. Neoplasia can occur, similar to the type of neoplasia that is observed in classical adenomas (intestinal type neoplasia) or serrated neoplasia. The proportion of lesions with neoplasia can increase to more than 30% in the larger serrated lesions (Burgess et al., 2016). These lesions very often carry a *BRAF* mutation and often show the CpG island methylator phenotype, with promoter methylation of *hMLH1*, causing microsatellite instability (Bettington et al., 2017). The interobserver variation between pathologists is particularly high for these lesions (Ensari et al., 2012; Rau et al., 2014), probably because they are part of a spectrum with hyperplastic polyps. The risk of progression of a sessile serrated lesion to CRC is highest for neoplastic lesions, and the 10-year cumulative risk of developing CRC was reported to be 4.4% for patients diagnosed with a sessile serrated lesion with neoplasia (Erichsen et al., 2016).

The third type of serrated lesions and polyps, the traditional serrated adenoma, is rare and accounts for 0.5–2.5% of all colorectal polyps. The most distinctive features are the slit-like serration, tall columnar cells with intensely eosinophilic cytoplasm and pencillate nuclei, and ectopic crypt formations along villous projections. These polyps frequently carry *KRAS* mutations (Bettington et al., 2015). In patients with a traditional serrated adenoma, the risk of developing advanced adenoma or CRC is more than twice that in patients with a classical adenoma, and the 10-year cumulative risk of developing CRC was reported to be 4.5% (Yoon et al., 2015; Erichsen et al., 2016).

1.2.3 Colorectal cancer

Classification of CRC is traditionally performed according to the histological subtypes as defined by WHO (WHO Classification of Tumours Editorial Board, 2019). The most common subtype is adenocarcinoma not otherwise specified, which accounts for 85% of CRC cases worldwide. The second most common subtype is mucinous carcinoma, which is characterized by the presence of mucinous lakes in at least 50% of the tumour area and accounts for 5–20% of CRC cases worldwide (Hugen et al., 2014). Previously, mucinous carcinoma had always been considered to be associated with a poor prognosis, but this no longer seems to be the case (Hugen et al., 2016). Recently, medullary carcinoma has been increasingly identified, and its frequency has been estimated to be 4% (Nagtegaal & Hugen, 2015). This subtype is characterized by solid growth in combination with an inflammatory reaction. Medullary carcinomas are almost invariably microsatellite instable, most frequently in combination with *BRAF* mutations (WHO Classification of Tumours Editorial Board, 2019), and the prognosis of patients with these tumours is excellent. Signet-ring cell carcinomas are relatively rare in the colon, with a reported frequency of less than 2%, and are associated with a very poor outcome (Hugen et al., 2015).

CRC can also be classified according to its location. The difference between colon cancer and rectal cancer has long been recognized, mainly because of the differences in treatment options, and recently it has garnered more interest because of the variation in possible screening modalities. However, the division of colon cancer by embryological origin (midgut or proximal colon and hindgut or distal colon) also seems relevant for outcomes, given the differences in biology and behaviour. Distal colon cancer is associated with better outcomes than proximal colon cancer, even after correction for stage (Petrelli et al., 2017).

Molecular classifications are increasingly important. Microsatellite instability is considered to be the second most common molecular pathway for the development of CRC, the first being the adenoma–carcinoma pathway involving *APC* mutations (see Fig. 1.6). In addition to being the result of germline mutations in Lynch syndrome, microsatellite instability is present in up to 20% of sporadic CRC as well (Li et al., 2013). The majority of tumours with microsatellite instability have hypermethylation of *hMLH1*, which is more commonly found in the proximal colon in elderly women (Li et al., 2013). There is an overrepresentation of mucinous carcinoma and medullary carcinoma in the group with microsatellite instability, and when restricted to early-stage disease, the prognosis of patients with these tumours is excellent.

A more complex molecular classification is that based on the findings of a large international consortium that was formed to solve the complex issue of multiple gene expression-based classifications of CRC (Guinney et al., 2015). This classification identifies five different groups: consensus molecular subtype 1 (CMS1) (microsatellite instable, immune activation), CMS2 (canonical), CMS3 (metabolic), CMS4 (mesenchymal), and a mixed group that cannot be further classified.

1.3 Stage at diagnosis, survival, and treatment

1.3.1 Stage at diagnosis

The staging system used for CRC is the tumour–node–metastasis (TNM) classification, which is based on the original publication by Dukes (Dukes, 1932). The T refers to the extent of invasion depth of the tumour in the various layers of the bowel wall (T1, submucosa; T2, muscularis propria; T3, mesocolic or mesorectal fat; and T4, perforation of serosa or ingrowth in other organs). The N refers to the number of lymph nodes involved (N0, no involved lymph nodes; N1, 1–3 nodes involved; and N2, 4 or more nodes involved) (Sobin, et al., 2009). Recently, a special nodal category, N1c, was created to indicate the presence of tumour deposits in the absence of lymph node metastases; this has been subject to much debate in the literature (Nagtegaal et al., 2012, 2017), which complicates treatment choices. The M refers to the presence of distant metastasis (M0, no distant metastasis; M1, metastasis beyond regional lymph nodes).

The T, N, and M stages are combined into the stage classification. The stages for CRC are as follows: stage I is early-stage cancer that is limited to the bowel wall (T1, T2) and without lymph node metastases; stage II is cancer without lymph node metastases and T3–T4 tumours; stage III is cancer without distant metastases but with lymph node metastases; and stage IV is cancer with distant metastases (M1) at diagnosis. The T, N, and M stages are not independent. With increasing T stage, the risk of lymph node metastases and distant metastases increases, and with increasing N stage, the risk of distant metastases also increases. Tis, which refers to carcinoma in situ, is not considered to be cancer but should be regarded as high-grade neoplasia (Bosman et al., 2010).

Stage at diagnosis is influenced by multiple factors and varies widely. Because not all cancer registries routinely report these data, few large-scale studies are available. Also, several studies have reported using a three-tiered system, consisting of localized disease (TNM stages I and II), regional spread (TNM stage III), and distant spread (TNM stage IV). It is difficult to compare studies from different periods and locations, because many factors may be responsible for the reported differences, including treatment strategies, age distribution of the population, access to health care, diagnostic options, and the quality of the registration and the diagnostic workup. Improved diagnostic possibilities may increase the number of stage IV cancers, because as the resolution of imaging techniques increases, a greater number of and smaller distant metastases may be detected. Table 1.2 summarizes stage distribution at diagnosis in population data that were collected predominantly before the full implementation of organized population screening programmes. Early detection of cancer, as a result of population screening programmes, opportunistic screening, increased awareness, and surveillance programmes for high-risk patients, may result in lower stages at diagnosis. Indeed, pilot studies, trials, and population-based investigations have shown an increase in the number of early-stage cancers, with a concomitant decrease in the number of stage IV cancers (Lindebjerg et al., 2014; Yang et al., 2014; Binefa et al., 2016; Kubisch et al., 2016).

1.3.2 Survival

The relationship between stage and outcome is evident: the higher the tumour stage, the shorter the survival time. Although almost all individual studies show this effect, there is a relative shortage in the literature on the comparison of stage-dependent outcomes in larger cohorts worldwide (Table 1.3 and Table 1.4). A recent study comparing outcomes in six high-income countries showed evident differences, with the

Table 1.2 Stage distribution of colorectal cancer at the time of diagnosis, by country or region and time period

Country or region	Cancer site	Period of diagnosis	Stage at diagnosis (%)				Reference
			I	II	III	IV	
Northern Europe	Colorectum	1996–1998	12	33	20	11	Allemani et al. (2013)
Western Europe	Colorectum	1996–1997	16	32	22	18	Allemani et al. (2013)
Southern Europe	Colorectum	1996–1998	14	30	24	20	Allemani et al. (2013)
Eastern Europe	Colorectum	1996–1998	26	24	14	30	Allemani et al. (2013)
Denmark	Colon	2004–2007	11	30	27	31	Maringe et al. (2013)
Sweden	Colon	2000–2007	11	37	29	23	Maringe et al. (2013)
United Kingdom	Colon	2000–2007	9	39	35	17	Maringe et al. (2013)
Canada	Colon	2004–2007	18	31	26	26	Maringe et al. (2013)
USA registries	Colorectum	1997	17	28	38	10	Allemani et al. (2013)
Sub-Saharan Africa	Colorectum	Not reported	6	57	31	6	Graham et al. (2012)
Islamic Republic of Iran	Colorectum	2002–2007	7	32	32	16	Moghimi-Dehkordi et al. (2008)
China	Colorectum	1980s	13	30	36	21	Li & Gu (2005)
China	Colorectum	1990s	11	37	37	15	Li & Gu (2005)
Japan	Colon	1974–1993	12	37	28	19	Muto et al. (2001)
South Australia	Colorectum[a]	2003–2008	20	30	28	14	Beckmann et al. (2016)

[a] Only populations between age 50 years and age 79 years are included.

Table 1.3 Stage-related survival of colorectal cancer using four-tiered staging

Country (data source)	Cancer site	Period of diagnosis	Survival by stage of disease (%)				Follow-up	Reference
			I	II	III	IV		
Australia	Colorectum[a]	2003–2008	95	84	62	9	5-year survival	Beckmann et al. (2016)
Canada	Colon	2004–2007	94	87	71	13	3-year survival	Maringe et al. (2013)
Denmark	Colon	2004–2007	89	87	67	13	3-year survival	Maringe et al. (2013)
Europe (EUROCARE)	Colorectum	1990–1991	93	85	53	16	3-year survival	Ciccolallo et al. (2005)
Japan	Colon	1990–1992	94	90	82	16	5-year survival	Muto et al. (2001)
Sweden	Colon	2000–2007	98	91	69	16	3-year survival	Maringe et al. (2013)
United Kingdom	Colon	2000–2007	95	85	58	12	3-year survival	Maringe et al. (2013)
USA (SEER)	Colorectum	1990–1991	94	89	63	16	3-year survival	Ciccolallo et al. (2005)

EUROCARE, European Cancer Registry-based Study on Survival and Care of Cancer Patients; SEER, Surveillance, Epidemiology, and End Results.

[a] Only populations between age 50 years and age 79 years are included.

Table 1.4 Stage-related survival of colorectal cancer using three-tiered staging

Country (region or data source)	Cancer site	Period of diagnosis	Survival by stage of disease (%)			Follow-up	Reference
			Local	Regional	Distant		
Australia	Colon	2000–2007	93	75	20	3-year survival	Maringe et al. (2013)
Canada	Colon	2004–2007	92	70	13	3-year survival	Maringe et al. (2013)
Cuba	Colon	1994–1995	65	45	21	5-year survival	Sankaranarayanan et al. (2011)
Denmark	Colon	2004–2007	90	68	13	3-year survival	Maringe et al. (2013)
India (Mumbai)	Colon	1987–1991	61	32	9	5-year survival	Yeole et al. (2001)
Islamic Republic of Iran (Golestan)	Colorectum	2004–2007	81	52	0	5-year survival	Aryaie et al. (2013)
Norway	Colon	2000–2007	91	77	14	3-year survival	Maringe et al. (2013)
Philippines (Manila)	Colon	1994–1995	69	34	0	5-year survival	Sankaranarayanan et al. (2011)
Republic of Korea	Colorectum	2006–2010	93	78	18	5-year survival	Jung et al. (2013)
Sweden	Colon	2000–2007	93	69	16	3-year survival	Maringe et al. (2013)
Singapore	Colon	1993–1997	67	43	7	5-year survival	Sankaranarayanan et al. (2011)
Thailand (Lampang)	Colon	1990–2000	60	57	2	5-year survival	Sankaranarayanan et al. (2011)
Turkey (Izmir)	Colon	1995–1997	60	54	21	5-year survival	Sankaranarayanan et al. (2011)
United Kingdom	Colon	2000–2007	87	59	12	3-year survival	Maringe et al. (2013)
USA (SEER)	Colorectum	1975–1977	82	52	6	5-year survival	Jemal et al. (2017)
USA (SEER)	Colorectum	2006–2012	91	73	14	5-year survival	Jemal et al. (2017)

SEER, Surveillance, Epidemiology, and End Results.

lowest stage-corrected survival in the United Kingdom (Maringe et al., 2013).

1.3.3 Treatment

Treatment advice is dependent on the stage of disease. The decision about whether to administer neoadjuvant treatment is based on the stage determined by imaging. In particular, an advanced T stage in rectal cancer is an indication for neoadjuvant radio(chemo)therapy. Other treatment decisions are based on pathological staging. For early pT1 cancers, the risk of lymph node metastases is low and local treatment may therefore be sufficient. For a more balanced risk evaluation in those patients, additional histological biomarkers are usually included in the discussion (Bosch et al., 2013). When only tumour stage is taken into consideration, adjuvant chemotherapy is usually advised for patients with stage III disease, as well as for high-risk patients with stage II disease (Benson et al., 2004). For patients with stage IV disease, a personalized approach is chosen, which varies between the resection of limited metastatic disease and palliative systemic therapy and combinations thereof. In general, treatment decisions are made at multidisciplinary team meetings.

1.4 Risk factors and protective factors

Unlike for some other cancers, such as those of the lung or the skin, there is no single risk factor that accounts for most cases of CRC. Factors associated with high relative risks, such as inherited conditions, are uncommon and are

Table 1.5 Established risk factors for colorectal cancer and associated relative risk

Risk factor	Categories	RR (95% CI)	Reference
Consumption of processed meat	Per 50 g/day	1.16 (1.08–1.26)	WCRF/AICR (2017)
Alcohol consumption	Per 10 g/day of ethanol	1.07 (1.05–1.08)	WCRF/AICR (2017)
Body fatness	Per 5 kg/m² of BMI	Colorectum: 1.05 (1.03–1.07) Colon: 1.07 (1.05–1.09) Rectum: 1.02 (1.01–1.04)	WCRF/AICR (2017)
Abdominal fatness	Per 10 cm of waist circumference	1.02 (1.01–1.03)	WCRF/AICR (2017)
Tobacco smoking	Never smokers Current smokers Former smokers	1.00 1.15 (1.00–1.32) 1.20 (1.04–1.38)	IARC (2012)
Attained adult height	Per 5 cm	1.05 (1.02–1.07)	WCRF/AICR (2017)
Sex[a]	Female Male	1.00 1.47	Ferlay et al. (2018a)
Age[a]	45–49 yr 50–54 yr 55–59 yr 60–64 yr 65–69 yr ≥ 70 yr	1.00 1.75 2.85 4.33 6.30 10.29	Ferlay et al. (2018a)

BMI, body mass index; CI, confidence interval; RR, relative risk; yr, years.
[a] Calculated by the Working Group from GLOBOCAN 2018 incidence figures.

often non-modifiable, so that most of the disease burden at the population level is attributable to factors associated with lower relative risks, many of which are potentially modifiable.

Here, risk factors and protective factors are broadly grouped into three types: lifestyle and environmental factors, host factors, and use of medications. The relative magnitudes of the effects associated with these risk factors and protective factors, based on the most recent systematic reviews and meta-analyses, are presented in Table 1.5 and Table 1.6, respectively. Factors associated with a high predisposition to CRC, which usually require close medical surveillance of the people with such risk factors outside population screening, are addressed in Section 3.8.

1.4.1 Lifestyle and environmental factors

(a) Diet

Food and nutrition play an important role in the prevention and the causation of CRC. Established risk factors are presented in Table 1.5.

There is sufficient evidence that consumption of processed meat increases the risk of CRC (WCRF/AICR, 2017; IARC, 2018a), with strong evidence of the mechanisms operating in humans (IARC, 2018a). [The differences in the assessment of processed meat consumption across studies included in meta-analyses should be kept in mind.] Consumption of alcoholic beverages increases the risk of CRC, with a monotonic dose-dependent relationship above 30 g/day (about two drinks per day) (IARC, 2012; Scoccianti et al., 2015; WCRF/AICR, 2017); the risk is greater in men than in women, and is similar for wine, beer, and spirits. The mechanisms of carcinogenesis operating in humans have been well established (IARC, 2012).

Table 1.6 Established protective factors for colorectal cancer and associated relative risk

Protective factor	Categories	RR (95% CI)	Reference
Consumption of dietary fibre	Per 10 g/day	0.91 (0.88–0.94)	WCRF/AICR (2017)
Consumption of whole grains	Per 90 g/day	0.83 (0.78–0.89)	WCRF/AICR (2017)
Consumption of dairy products	Per 400 g/day	0.87 (0.83–0.90)	WCRF/AICR (2017)
Milk intake	Per 200 g/day	0.94 (0.92–0.96)	WCRF/AICR (2017)
Calcium intake (dietary or supplemented)	Per 300 mg/day	0.92 (0.89–0.95)	Keum et al. (2014)
Physical activity (total level)	Low High	1.00 0.81 (0.69–0.95)[a]	WCRF/AICR (2017)
Aspirin use	Never use Ever use Per 325 mg/day Per 7 times weekly Per 10 years of use	1.00 0.74 (0.64–0.83) 0.80 (0.74–0.88) 0.82 (0.78–0.87) 0.82 (0.78–0.86)	Ye et al. (2013)
Hormone replacement therapy use	Never use Ever use Current use Former use	1.00 0.84 (0.81–0.88) 0.77 (0.73–0.82) 0.89 (0.84–0.95)	Green et al. (2012)

CI, confidence interval; RR, relative risk.

[a] A protective effect has been found for colon cancer (RR, 0.80; 95% CI, 0.72–0.88) but not for rectal cancer (RR, 1.04; 95% CI, 0.92–1.18).

Consumption of red meat probably increases the risk of colorectal cancer (WCRF/AICR, 2017; IARC, 2018a). In addition, there is suggestive evidence that consuming foods containing haem iron increases the risk of CRC (WCRF/AICR, 2017).

Consuming foods containing dietary fibre, especially whole grains, probably decreases the risk of CRC, with dose–response relationships (Table 1.6) (Aune et al., 2011; Norat et al., 2015; WCRF/AICR, 2017). The protective effect appears to be more robust for fibre from grains than for other sources of fibre (i.e. fruits and vegetables) (IARC, 2003). Consumption of dairy products (total dairy, milk, cheese, and dietary or supplemented calcium intakes) is also probably protective against CRC, with a clear dose–response relationship (WCRF/AICR, 2017). The effect is likely to be mediated by calcium (Keum et al., 2014), for which evidence of a protective effect is probable (WCRF/AICR, 2017). [Most of the evidence comes from high-income countries, where dietary calcium intake can be used as a marker for dairy consumption.] Calcium intake also decreases the risk of adenomas, particularly advanced adenomas, over a wide range of calcium intake, with a clear dose–response relationship (Keum et al., 2015). Evidence for a protective effect of eating non-starchy vegetables and fruits, fish, foods containing vitamin C, and foods containing vitamin D, and of taking multivitamin supplements is suggestive, based on reasonably consistent but still limited data (WCRF/AICR, 2017).

(b) Body fatness and abdominal fatness

There is sufficient evidence of an increased risk of CRC with increasing body fatness and abdominal fatness, with clear dose–response relationships and strong mechanistic data (Anderson et al., 2015; Lauby-Secretan et al., 2016; WCRF/AICR, 2017; IARC, 2018b). The effect is greater for colon cancer than for rectal cancer and, for body fatness only, is larger for men than for women (Harriss et al., 2009; WCRF/AICR, 2017). Although an unhealthy weight is often considered to be a result of potentially modifiable individual choices, it is now recognized that an obesogenic environment (i.e. sociocultural, economic, and marketing influences) poses challenges to the achievement of a healthy lifestyle (Kopelman, 2007; Mackenbach et al., 2014).

(c) Physical activity

Physical activity reduces the risk of colon cancer (IARC, 2002; WCRF/AICR, 2017). The protective effect appears to be slightly greater for recreational activity than for occupational physical activity (Mahmood et al., 2017). Two recent meta-analyses estimated similar decreases in risk of proximal and distal colon cancers among the most physically active compared with the least active individuals (Boyle et al., 2012; Robsahm et al., 2013). In contrast, physical activity appears to be unrelated to the risk of rectal cancer (Robsahm et al., 2013; WCRF/AICR, 2017). Cohort studies have shown that the beneficial effect of physical activity is independent of BMI (Leitzmann et al., 2015). Overall, there is a dose–response relationship with risk reduction across a wide range of the frequency and intensity of physical activity, and exercise does not need to be intense or long-lasting to have substantial benefits.

(d) Tobacco smoking

There is sufficient evidence that tobacco smoking causes CRC, with comparable increases in risk in current and former smokers (IARC, 2012). Dose–response studies also clearly demonstrate that the risk of CRC increases with increasing intensity and duration of smoking. The risk is consistently higher for rectal cancer than for colon cancer (Liang et al., 2009).

1.4.2 Host factors

(a) Attained height

There is convincing evidence that genetic, environmental, hormonal, and nutritional factors that lead to greater linear growth and greater attained adult height cause CRC, with a clear dose–response relationship (WCRF/AICR, 2017). The association between adult attained height and risk of CRC is stronger for women than for men and is stronger for colon cancer than for rectal cancer. Nutrition during early life, hormone profiles, and sexual maturation are likely to be relevant.

(b) Sex

There is a 1.47 male-to-female ratio of incidence rates for CRC worldwide, and the excess risk for men is observed in almost all regions (Ferlay et al., 2018a). The male–female disparity in the age-related risk of CRC is probably due to sex differences in the exposure to (and, to a lesser extent, in the effects of) risk factors such as lifestyle, diet, smoking, and obesity. Interactions between estrogen exposure, body fat distribution, and the biological underpinnings of colorectal tumours also may explain this sex-related difference as well as the higher proportion of proximal colon cancers in women than in men (Chacko et al., 2015).

(c) Age

In many populations, the incidence rates of CRC are relatively low in people younger than 50 years (accounting for ~10% of cases) but increase strongly with age (Ferlay et al., 2018a) (see also Section 1.1). Worldwide, the risk of developing CRC increases by a factor of about 1.5 between each successive 5-year age group in the age range 45–74 years, with some variations across populations (Ferlay et al., 2018a).

(d) Ethnicity

The factors underlying the substantial ethnic and racial disparities in the risk of and subsite distribution of CRC are multiple and complex, and these disparities are only partly attributable to differences in the prevalence of exposure to risk factors (Ollberding et al., 2011). Differences in genetic susceptibility and gene–environment interactions contribute to explain the disproportionately high risk of CRC worldwide in

Ashkenazi Jews (lifetime risk up to 15%) (Locker & Lynch, 2004) and the higher risk in Black and Asian people compared with White and Latino people (Ollberding et al., 2011). Compared with White people, Black people are more likely to have CRC diagnosed at an advanced stage and to have proximal CRC (Ollberding et al., 2011).

1.4.3 Use of medications

(a) Aspirin and other non-steroidal anti-inflammatory drugs

The evidence from follow-up of randomized trials (after about 20 years) and from observational studies demonstrates that long-term, low-dose, and regular use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) effectively reduces the risk of CRC in average-risk individuals (Rothwell et al., 2010; Huang et al., 2015). The dose–risk and duration–risk relationships between regular use of aspirin and CRC risk show that even low-dose (≤ 75 mg/day) and low-frequency (twice a week) intake of aspirin has a benefit, with a levelling off for a frequency of more than 7 times per week (Ye et al., 2013). However, the greater risks of developing ulcers, serious ulcer complications, and cardiovascular events associated with regular use of aspirin limit its potential for chemoprevention of CRC.

(b) Hormone replacement therapy

Results from meta-analyses consistently show that the use of hormone replacement therapy (HRT) is associated with a reduced risk of CRC (Friis et al., 2015). The reduction in risk is larger among current users of HRT than among former users, and, to a lesser degree, with increasing duration of use (Green et al., 2012; Johnson et al., 2013). Questions remain about how long the preventive benefits of HRT persist after use is discontinued. Although the use of HRT has benefit in reducing the risk of developing CRC, the potential harms, including increased risks of cardiovascular disease and gynaecological cancers, make the use of HRT unsuitable for primary prevention in women in the general population (Friis et al., 2015).

(c) Other medications

Randomized controlled trials (RCTs) showed a substantial reduction in the risk of developing colorectal adenomas and advanced adenomas over a 3-year follow-up period with use of cyclooxygenase-2 (COX-2) inhibitors (Rostom et al., 2007). Like NSAIDs, these chemopreventive agents are associated with increased risks of adverse cardiovascular outcomes and gastrointestinal harms.

A meta-analysis of five observational studies indicated a protective effect of metformin treatment against CRC in patients with type 2 diabetes (Zhang et al., 2011), and in one short-term RCT using aberrant crypt foci as endoscopic surrogate markers, a protective effect has also been suggested in people without diabetes (Hosono et al., 2010). The common side-effects of metformin include diarrhoea, nausea, and abdominal pain.

(d) Dietary supplements

In a meta-analysis of 20 prospective observational studies, dietary or supplemented calcium intake has been shown to reduce the risk of CRC, with a linear dose–response relationship (Keum et al., 2014). However, RCTs have not shown a consistent protective effect against CRC (Keum et al., 2017; WCRF/AICR, 2017). To date, RCTs of other dietary supplement interventions have not demonstrated a protective effect (Norat et al., 2015). Studies with folic acid (folate), beta-carotene, selenium, and vitamin D supplementation yielded null findings, sometimes with an unexpected increased risk of other types of cancer. Use of dietary supplements for CRC chemoprevention is not currently recommended.

1.4.4 Etiological differences by subsite

Some etiological and biological differences exist between CRC subsites (Lee et al., 2017). Risk factors such as BMI and height are more important for colon cancer than for rectal cancer, whereas tobacco smoking may influence the risk of rectal cancer more than that of colon cancer (WCRF/AICR, 2017). Physical activity appears to influence the risk of colon cancer but not that of rectal cancer. Differences in embryological sources and physiological functions, affecting bile-acid metabolism, faecal composition, and transit time, have been advanced to explain these etiological differences between subsites. Neither differences related to subsite nor sex-related differences in the magnitude of risk are considered in Table 1.5 and Table 1.6.

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