2.4 Excess body fatness in cancer survivors

2.4.1 Studies of weight at diagnosis and cancer outcomes

An increasing number of observational studies are focusing on the association between excess body fatness and prognosis in cancer survivors. Specifically, more than 100 individual reports have evaluated the relationship between BMI or body weight at the time of diagnosis of early-stage breast cancer and the risk of breast cancer recurrence, breast cancer-related mortality, and all-cause mortality.

A meta-analysis of 82 reports on this topic (all but 8 of which had a median follow-up of at least 5 years) incorporated data from 213 075 women (Chan et al., 2014). Women who were obese (BMI > 30.0 kg/m^2) at the time of diagnosis of breast cancer had a 35% increased risk (RR, 1.35; 95% CI, 1.24–1.47) of breast cancer-related mortality and a 41% increased risk of all-cause mortality compared with women who were of normal weight at the time of breast cancer diagnosis. The association between obesity and poor outcomes was seen in both postmenopausal and premenopausal breast cancer survivors, with summary relative risks for all-cause mortality in obese versus normal-weight women of 1.75 (95% CI, 1.26–2.41) in women with premenopausal breast cancer and 1.34 (95% CI, 1.18–1.53) in women with postmenopausal breast cancer.

In another study, the WCRF Continuous Update Project reviewed data on the association in female breast cancer survivors between weight and the risk of dying of breast cancer, second cancers, or any cause (WCRF/AICR, 2014). The report stressed the importance of taking into account the timing of weight measurement, focusing on three main time points: (i) before diagnosis; (ii) less than 12 months after diagnosis; and (iii) more than 12 months after diagnosis. Associations were observed between measures of adiposity and prognosis, but there were many pitfalls to interpretations, biases, and confounding. The evidence linking obesity to cancer survival was rated as "limited-suggestive", primarily because of concerns about the timing of baseline BMI analysis in relation to cancer diagnosis in some studies.

Fewer studies have evaluated the association between body fatness and cancer prognosis in other malignancies. A meta-analysis that evaluated the relationship between obesity and colorectal cancer outcomes included 16 reports that encompassed 58 917 individuals followed up for a median of 9.9 years (Lee et al., 2015). Obesity before diagnosis of colorectal cancer was associated with an increased risk of colorectal cancer-specific mortality (RR, 1.22; 95% CI, 1.00–1.35) and all-cause mortality (RR, 1.25; 95% CI, 1.14–1.36). Obesity after diagnosis of colorectal cancer was also associated with an increased risk of all-cause mortality (RR, 1.08; 95% CI, 1.03–1.13).

Excess body fatness has also been linked with biochemical recurrence of cancer (rising levels of prostate-specific antigen [PSA]) in men with early-stage prostate cancer treated with radical prostatectomy or external beam radiation. A meta-analysis of 26 studies, including 36 927 men, estimated a 16% increase in the risk of elevated PSA levels with each 5 kg/m^2 increase in BMI (RR, 1.16; 95% CI, 1.08–1.24) (Hu et al., 2014).

A meta-analysis of 14 studies that assessed BMI before or shortly after diagnosis in women with ovarian cancer estimated a hazard ratio for all-cause mortality of 1.17 (95% CI, 1.03–1.34) for obese versus non-obese patients (Protani et al., 2012). Another meta-analysis of 13 cohort studies of individuals with pancreatic cancer reported an adjusted hazard ratio for pancreatic cancer-related mortality of 1.06 (95% CI, 1.02–1.11) in overweight patients and of 1.31 (95%

CI, 1.20–1.42) in obese patients versus normal-weight patients (Majumder et al., 2015).

Meta-analyses and/or systematic reviews on obesity and cancer survival have also been conducted in patients with endometrial cancer (Arem & Irwin, 2013; Nakao et al., 2014) and with childhood leukaemia (Amankwah et al., 2015).

[It is unclear whether the relationship between obesity and increased risk of cancer-related mortality stems from differences in the biological aggressiveness or subtypes of cancers that develop in obese versus non-obese patients. Some studies have suggested that obese individuals are more likely to develop biologically aggressive cancers with poorer outcomes, or to have more advanced disease at the time of diagnosis. For example, studies have shown that obese individuals are at increased risk of developing biologically aggressive prostate cancers, but not of developing lower-grade prostate cancers (see Section 2.2.14). Some reports suggest that obese women are more likely to develop poorly differentiated and hormone receptor-negative breast cancers (Stark et al., 2010; Abdel-Maksoud et al., 2012), although other reports suggest that obese women are more likely to develop slower-growing hormone receptor-positive breast cancers (Borgquist et al., 2009; Canchola et al., 2012; Biglia et al., 2013). A few recent studies that have used genomic profiling techniques have suggested that obese women who develop hormone receptor-positive cancers are more likely to have luminal B cancers, which have been shown to have a worse prognosis, compared with luminal A cancers (Kwan et al., 2015; Ligibel et al., 2015). See Section 2.2.9 for more detailed data on risk estimates by subtype of breast cancer.]

2.4.2 Studies of weight change after cancer diagnosis and cancer outcomes

Fewer studies have investigated the association between weight change after cancer diagnosis and recurrence-free or overall survival.

A recent meta-analysis of 12 studies examined the association between weight gain after diagnosis of breast cancer and prognosis (Playdon et al., 2015). High weight gain after breast cancer diagnosis (> 10% of body weight at diagnosis) increased the risk of both all-cause mortality and breast cancer-specific mortality, whereas moderate weight gain (5–10%) did not (HR, 0.98; 95% CI, 0.83–1.15). The increased risk was observed among women with a BMI at diagnosis of less than 25 kg/m^2 and of 25 kg/m^2 or more. In an earlier analysis of a prospective cohort study of 5204 non-smoking women with early-stage breast cancer, those who gained more than 2 kg/m^2 had a significantly increased risk of death from breast cancer compared with women who maintained a stable weight; the relative risk of death from breast cancer was 1.35 (95% CI, 0.93–1.95) for weight gain of 0.5–2 kg/m^2 and 1.64 (95% CI, 1.07–2.51) for weight gain of more than 2 kg/m^2 (Kroenke et al., 2005). In contrast, in another study of 1692 women with early-stage breast cancer, no association was observed between weight gain and breast cancer recurrence or all-cause mortality, even among women who gained more than 10% of their baseline body weight (Caan et al., 2006).

2.4.3 Intervention trials of weight-loss intervention and dietary modification

No data were available to the Working Group about the impact of a weight-loss intervention on cancer recurrence, cancer-related mortality, or all-cause mortality in cancer survivors.

Two randomized trials assessed the impact of dietary modification on disease-free and overall survival in women with early-stage breast cancer.

The Women's Intervention Nutrition Study randomized 2400 women to a low-fat dietary intervention or usual care (control group) (Chlebowski et al., 2008). Patients assigned to the intervention group reduced their dietary fat intake for the duration of the 5-year intervention.

Intervention participants experienced an average weight loss of 6 lb (2.7 kg). An initial analysis of study results demonstrated a 24% reduction in breast cancer recurrence compared with the control group (HR, 0.76; 95% CI, 0.60–0.98) (Chlebowski et al., 2006), although the difference lost statistical significance with further follow-up (Chlebowski et al., 2008). Unplanned subset analysis suggested that the impact of the intervention differed in women with ER-positive cancers versus those with ER-negative cancers, with a hazard ratio for recurrence in the intervention group versus controls of 0.58 (95% CI, 0.37–0.91) in women with ER-negative cancers and 0.85 (95% CI, 0.63–1.14) in women with ER-positive cancers ($P_{interaction} = 0.15$). [The weight loss experienced by participants in the Women's Intervention Nutrition Study may have contributed to the reduced risk of cancer recurrence in intervention participants in that study.]

In contrast, the Women's Healthy Eating and Living study randomized 3088 women to a counselling programme for a diet very high in fruits and vegetables and low in fat or printed guidelines (Pierce et al., 2007). Adherence to the dietary intervention was good, with intervention participants increasing their daily intake of vegetables by 65% and of fruits by 25%, and reducing their daily intake of fat by 13%. [Of note, participants consumed on average seven servings of fruits and vegetables per day at baseline.] Participants randomized to the dietary intervention group did not lose weight compared with controls. The dietary intervention had no impact on rates of recurrence (HR for recurrence in intervention group vs controls, 0.96; 95% CI, 0.80–1.14).

[There were several differences between the trials, including in the degree of reduction in dietary fat intake achieved by intervention participants, the baseline diets, the delivery method of the dietary intervention, the timing of enrolment relative to breast cancer diagnosis, and the study population.]

Several ongoing studies are testing the hypothesis that weight loss after cancer diagnosis reduces the risk of cancer recurrence or progression in individuals with early-stage cancer (Courneya et al., 2008; Rack et al., 2010; Villarini et al., 2012; Crane et al., 2014; Parsons et al., 2014).

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