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GCSF usage.

...patient-related risk factors for FEN, in addition to the well-known FEN risk of the chemotherapeutic regimens.

The multivariable analysis of Chao et al. showed us similar risk factors that have been defined in the literature. As a result of the retrospective design, these studies have some inevitable limitations. Concomitant radiotherapy history is an important predictive of neutropenia. Especially, radiotherapy to vertebral column or pelvis is an important risk factor for FEN because these bones compromise nearly 40% of the bone marrow reservoir in adult [3]. Radiotherapy history must have been included in multivariable analysis. The other important factor that sometimes provokes the chemotherapy induced neutropenia is deficiency of folate and vitamin B12. Peptic ulcer disease has defined as a risk factor with a hazard ratio of 1.57 in the analysis. The coincidental presence of atrophic gastritis with defined peptic ulcer disease causing decreased fuel for hematopoiesis may be the reason of increased risk for FEN. The inclusion of deficiencies and replacement therapies to analysis may have clarified this association. The other interesting finding was the decreased risk with obesity. Although, fat tissue is an important energy reservoir during trauma, the distribution of different chemotherapeutics in fat tissue, and as a result, effects on normally functioning organs may differ. Additional factors such as chemotherapeutic agents used and their distribution properties, lean body mass and presence of sarcopenia which is important for defining frailty and body composition of the obese patients should be evaluated for better analysis. Reduced risk with obesity may also be a result of the decreased dosages of drugs used in regimens. Although studies have confirmed the safety of full weight based dosing, up to 40% of the obese patients have limited chemotherapeutic dosages [4]. So, inefficient therapy due to decreased doses may have led to decreased toxicity and also neutropenia. Obesity and question about its potential protective effect on FEN may be clarified with analysis of body surface areas and initial treatment dosages of the patients. The analysis of muscle and fat mass evaluation may give further information in obese patients.

The usage of GCSFs should not be managed only with the risk of the regimen. With well-defined risk factors, especially comorbidities and more complicated risk scores under the light of guidelines will help us for more efficient and cost-effective GCSF usage.

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The obesity and cancer link

The existence of a causal link between obesity and cancer incidence has been widely investigated and it could be considered to date not more a mere medical hypothesis but a consolidated biomedical research area. In the last years, indeed, numerous epidemiological evidences associating weight gain expressed in terms of a high body mass index (BMI) to occurrence of several tumors have been discussed and different molecular mechanisms have been proposed, although they are poorly understood yet, partially depending on cancer type. A large-scale study by Bhaskaran et al. on *Lancet* [1] strongly and unequivocally confirms BMI–cancer association across a range of sites in UK population. The risk of cancers of the endometrium, kidney, gallbladder and uterus were found increased in individuals being overweight or obese (BMI ≥25.0). Then Kaaks and Kühn on *Nature Reviews Endocrinology* analyzed this study affirming that questions remain as to whether several of the other recorded weaker associations reflect genuinely causal relationships and the necessity for epidemiologic studies to use more advanced measurements of overall and regional body composition [2]. Furthermore, two recently studies on *Cancer Research* show evidences supporting the critical roles played by adipose tissue in breast cancer pathogenesis and progression [3, 4] and one more study by Copson et al. just published on *Annals of Oncology*, analyzing data from a large British cohort study (the Prospective study of Outcomes in Sporadic versus Hereditary breast cancer, POSH study), observed the rising rates of obesity in patients with early breast cancer, which present adverse tumor characteristics, indicating that obesity was a significant independent predictor of overall survival and distant disease-free interval [5].

In our opinion, these evidences justify the introduction and the utilization in scientific community of the neologism ‘adiponcosis’ that we have designed to describe the concept that the accumulation of fat may induce cancer occurrence [6, 7]. Therefore, the American Society of Clinical Oncology (ASCO) has recently aimed at this link between Obesity and Cancer developing a strategy to reducing the impact of obesity on cancer risk and cancer-related mortality and the need to maintain a healthy weight [8]. Since obesity is a complex societal problem and the majority of people are unaware that it can increase the risk of cancer, ASCO indicated multipronged guidelines for the prevention of obesity-related cancers by promoting the education, research and policy changes needed to reduce the impact of obesity on public health and, in particular, on cancer risk and outcomes, establishing new partnerships between oncology and other obesity specialties. Further clinical or experimental evidences and research in this field, aimed to elucidate the molecular mechanisms linking obesity to cancer and to
characterize the beneficial pharmacological effects of compounds acting on their converging pathways, is, therefore, now an urgent call for researchers working in the field of obesity and cancer prevention and treatment.

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The harms of low-dose aspirin prophylaxis are overstated

We commend the authors of this paper for their exacting evaluation of the benefits of long-term low-dose aspirin on incidence vascular disease and cancer [1]. In 2008, a paper we published a paper with the title ‘Aspirin for everyone older than 50?’ [2]. This report by Cuzick et al. removes the need for a question mark!

Nevertheless, we are alarmed by the estimates Cuzick et al. make of the number of fatal internal bleeding attributable to aspirin, leading the media in the UK to refer to aspirin prophylaxis as ‘a lottery’. Evidence from community-based studies and from randomised, controlled trials shows that the estimate by Cuzick et al. of two extra deaths in 1000 individuals aged 60 who took low-dose aspirin for 10 years, is a gross overestimate if not a serious misinterpretation of available evidence.

With regard to gastrointestinal bleeding, the authors estimate that, under the age of 70 years, 5% of spontaneous gastrointestinal bleeds lead to death while, over the age of 70 years, they assume that 10% of spontaneous bleeds are fatal. The figure of 5% fatal bleeds is well supported by community-based studies, both in the general community and in selected subjects taking low-dose aspirin. Thus, in two community-based studies, the mortality rate from GI complications, which were mostly upper GI bleeding, was 5.7% and 5.6% [3]. In 3000 patients admitted to hospital because of adverse drug reactions (ADRs) to aspirin [4], 162 subjects had been taking low-dose aspirin and 7 of these (4.3%) had died. In the UK, a ‘Yellow Card Scheme’ (https://yellowcard.mhra.gov.uk) facilitates the reporting of ADRs by health care professionals and by members of the public. The degree of under-reporting in this scheme is unknown but is likely to be low for the most serious, life-threatening ADRs. Since 1963, 1572 gastrointestinal bleeds in patients taking low-dose aspirin have been reported, 60 (3.8%) of which were fatal [5].

The incidence of fatal GI bleeds reported in randomised trials is similar (5.2% and 4% [6–8] and the proportion of bleeds that are fatal is not increased in the subjects allotted to aspirin. Thus, in the Anti-Thrombosis Trialists’ overview [6], there were 9 fatal GI bleeds in subjects on aspirin and 20 in those on placebo, giving an odds ratio (OR) for a fatal bleed from aspirin of 0.48 (0.17, 1.34). Another report [7] states that deaths attributable to bleeding in subjects randomised to aspirin were 3.9 per 100 000 subjects per year and 5.1 per 100 000 per year in those on placebo, giving an OR of 0.79 [95% confidence interval (CI) 0.38–1.64]. In a long-term follow-up of 34 trials [8], 8 of 203 GI bleeds (4%) were fatal in subjects on aspirin, and 15 of 132 (11%) of those on placebo were fatal, an OR for aspirin of 0.32 (95% CI 0.12–0.83). In yet another review of 35 trials involving 87 000 subjects, the OR for a fatal bleed in patients randomised to aspirin was 0.94 (95% CI 0.47–1.87) [9].

Cerebral bleeding attributable to aspirin is rare and information on deaths is sparse. Hypertension is a major factor and in the antithrombosis trialists overview a rise of 20 mmHg in blood pressure was associated with a doubling of cerebral haemorrhage (risk ratio (RR) 2.18; 95% CI 1.65–2.87) [6]. The Hypertensive Optimal Treatment (HOT) trial [10], however, was based on patients with hypertensive disease, all of whom were optimally treated with antihypertensive drugs. There was no evidence of any extra cerebral bleeds in 10 000 patients randomised to aspirin (19 cerebral bleeds, 7 fatal) as in ten thousand on placebo (20 bleeds, 8 fatal).

Cuzick et al. include peptic ulceration when referring to fatal internal bleeds. Whether or not low-dose aspirin is ever responsible for peptic ulceration is uncertain. Gastric and intestinal mucosal damage can be seen on endoscopic examination following short-term aspirin administration, but this appears to improve rapidly during continued aspirin taking [11]. Although a ‘second wave’ of deeper mucosal injury has been described and can be responsible for blood loss, this too appears to heal with continued aspirin taking [12]. On balance therefore, it seems unlikely that aspirin is responsible for peptic ulceration let alone fatal ulceration [13].

Finally, estimates of bleeding attributable to aspirin should take account of a steady fall in risk over time. In an overview of 17 randomised studies, there was a fourfold risk of a bleed in subjects on aspirin during the first month (RR 4.4; 95% CI 3.2–6.1) and this then fell rapidly [14]. Data from the long-term follow-up of randomised trials take this further and while GI bleeding attributable to aspirin during the first 3 years of aspirin taking was almost double that, in subjects on placebo (OR 1.95; 95% CI 1.47–2.59), the risk reduced during the following 2 years and there was no significant excess in GI bleeding after 5 years on aspirin [15].