Ettore "Ted" DeGrazia. *Alone*. Oil on canvas, 10″ × 18″. Courtesy of DeGrazia Foundation.

The association between comorbidity and the risk and prognosis of cancer is reviewed.

Interaction Between Comorbidity and Cancer

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Background: *Older patients have an average of three comorbidities in addition to their cancer. Oncologic studies have usually ignored this aspect when adjusting for confounders. There is mounting evidence that comorbidity interacts with risk, survival, disease progression, and treatment of elderly patients with cancer. The strength of many of these interactions increases with age.*

Methods: *A review of the literature was undertaken regarding two of these interactions: cancer risk and prognosis.*

Results: *In older patients, the risk and behavior of cancer can be strongly affected by comorbidities and their related treatment. Rather than a blanket effect, this effect might be attached to groups of syndromes with common pathophysiologic mechanisms. This is notably true for metabolic disorders and inflammatory diseases.*

Conclusions: *In addition to focusing on the influence of cancer treatment on comorbidity or on the effect of comorbidity in delivering cancer treatment, future endeavors will need to consider the direct impact of comorbidity on the risk and the behavior of the cancer in elderly patients.*

Introduction

Age is the single most important risk factor for the development of cancer. A 20-year-old individual has approximately a 1/10,000 risk of developing a cancer per year. At 50 years of age, the risk is about 1/1000, and at age 80, it is about 1% per year. The mechanisms for this effect are hotly debated: time to accumulate mutations and epigenetic modifications, oxidative damage, modifications of the immune system, and decreased cell repair mechanisms have all been hypothesized. One aspect of aging, however, is an increased prevalence of comorbidity in general. Cancer patients aged 70 years and greater have on average three comorbidities.[1] These comorbidities can affect cancer risk, detection, evolution, and treatment. Increased comor-

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Abbreviations used in this paper: RR = relative risk, CI = confidence interval, OR = odds ratio, NHL = non-Hodgkin's lymphoma, IKKβ, = IκB kinase β, BMI = body mass index, SIR = standardized incidence ratio, SMR = standardized mortality ratio, NSAIDs = nonsteroidal anti-inflammatory drugs.

bidity is also associated with a parallel polymedication. At our center, older cancer patients take an average of six concomitant drugs.[2]

This article provides an overview of the recent data on the interaction of comorbidity and cancer. It also focuses on the direct interactions between the comorbidities, with their treatment, and the cancer as a disease (ie, the comorbidities as associated with the risk and prognosis of cancer). Another aspect of the interaction between comorbidities and cancer is how this interaction influences the treatment of cancer itself, which introduces the oncologist as a mediating agent. This topic would constitute material for an entire self-standing review and therefore is not addressed in this article. Also, a discussion of how the cancer modifies the risk, prognosis, and treatment of the other diseases is not included.

Comorbidity and the Risk of Cancer

The evidence in this category falls into two types. For some diseases, an association has been observed but no clear mechanism is available. For others, in vitro, animal, or human data supporting a direct mechanism of risk are available.

Metabolic Diseases

Diabetes and Metabolic Syndrome

The relationship between diabetes and cancer is the focus of much attention. This interest is often expanded to include the metabolic syndrome (also known as insulin resistance syndrome, or syndrome X).

The association of diabetes mellitus and cancer has received the most attention in the context of colorectal cancer. Diabetic patients have an increased incidence of colorectal cancer.[3-6] Insulin resistance below the diabetic level also appears to be associated with an increased risk of colon cancer. In a cohort of Chicago workers, subjects without diabetes but in the upper quartile in 3 out of 4 variables — post-load glucose, systolic blood pressure, body mass index, or resting heart rate — were at 1.5 the risk of colon cancer of others, a trend more marked in men.[7] A case control study of probands undergoing colonoscopy studied the association of colon cancer and adenomatous polyps with diabetes, hypertension, cardiovascular diseases, and hypercholesterolemia.[3] A significant association was observed, with the strongest effects being familial diabetes and hypertension. In stratified analyses, familial diabetes, hypertension, and strokes were significantly associated with adenomatous polyps in the subgroups of probands who were older and/or had symptoms at the time of colonoscopy. Only diabetes was possibly associated with colon cancer. Another study also found an increase in the strength of the association with age[4]; the association of diabetes with colon cancer was observed only in patients 60 years and older. A Japanese case control study showed that not only diabetes but also glucose intolerance was associated with an increased risk of colorectal adenomas.[8]

Diabetes also appears associated with an increased risk of breast cancer. In the Cancer Prevention Study II,[6] the relative risk (RR) of breast cancer was 1.27 (95% confidence interval [CI], 1.11–1.45). However, in a study by Weiss et al,[9] no significant association with breast cancer was found for diabetes, thyroid disease, gallbladder disease, colorectal polyps, high blood pressure, high cholesterol, or surgery for endometriosis in women less than 55 years of age. Some evidence of increased breast cancer risk was seen in women with ovarian cysts who did not receive oophorectomy (RR 1.94; 95% CI, 1.0–3.9). There was also a nonsignificant increase following diagnosis of other cancers.

Diabetics have long been known to have about a twofold increased risk of pancreatic cancer.[6,10] Recent studies suggest that the association is highest in the elderly and early after the diagnosis of diabetes. A Mayo clinic study[11] reviewed a population cohort of 2,122 patients diagnosed with diabetes at 50 years of age or older. Eighteen patients were diagnosed with pancreatic cancer within 3 years of diagnosis of diabetes, 10 within 6 months. Compared with Surveillance, Epidemiology, and End Results (SEER) data, the observed odds ratio (OR) of pancreatic cancer was 7.94 (95% CI, 4.70–12.55). In patients aged 70 years and older, it was 9.91 (95% CI, 5.26–16.96). New-onset diabetic patients with pancreatic cancer were more likely to have met diabetes criteria at age 70 years and older (OR 4.52; 95% CI, 1.61–12.74) than those aged 50 to 69 years. Unfortunately, only 3 proved resectable, but the series covers the years 1950 to 1995 and had no systematic screening for pancreatic cancer. Further targeting might lead to an even higher diagnosis rate of pancreatic cancer. In a series of 115 patients aged over 50 years who were hospitalized for unstable new-onset diabetes requiring insulin treatment, routine imaging detected abdominal disorder in 14 patients, 6 of which were pancreatic cancers.[12] Another series evaluated diabetic patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) for various indications.[13] When the ERCP was done within 3 years of the diagnosis of diabetes, the diagnosis of pancreatic cancer was made in 14% of the patients (5 in 36) compared with 1 in 50 after 3 years. Therefore, the diagnosis of pancreatic cancer was made in >1% of a general population of newly diagnosed diabetic patients 70 years of age and older, 5% of those hospitalized for it, and 14% of those undergoing an ERCP. Diabetes and pancreatic cancer might thus be linked in two ways:

diabetes as a risk factor for pancreatic cancer, and diabetes as a marker of pancreatic dysfunction secondary to the pancreatic cancer.

Diabetes has also been associated with an increased risk of liver cancer (RR 2.19; 95% CI, 1.76–2.72) and bladder cancer (RR 1.43; 95% CI, 1.14–1.80) in men.[6]

An Italian series observed an increased risk of Hodgkin's disease in patients with diabetes (OR 2.1).[14] This study also identified an increased risk of Hodgkin's disease in patients with a history of infectious mononucleosis (OR 4.0), herpes zoster (OR 2.9), pyelonephritis (OR 3.3), tuberculosis (OR 2.3), chronic bacterial diseases (OR 1.4), rheumatoid arthritis (OR 2.4), and psoriasis (OR 2.7). For non-Hodgkin's lymphoma (NHL), the OR was 2.9 for infectious mononucleosis, 1.8 for herpes zoster, 4.9 for pyelonephritis, 1.8 for tuberculosis, 1.9 for malaria, 1.7 for chronic bacterial diseases, 1.7 for rheumatoid arthritis, and 2.5 for psoriasis. Interestingly, most of these associations showed an age-related trend, with the association being stronger in elderly patients.

Several mechanisms have been postulated for the association of diabetes and the metabolic syndrome with cancer. The most frequently cited is insulin resistance. Insulin resistance has been associated with hyperinsulinemia, increased growth factors (including insulin-like growth factor [IGF]-1, activation of the NFκB antiapoptotic pathway via activation of the IκB kinase β (IKKβ), and activation of peroxisome proliferator-activated receptors.[15]

Other potential mechanisms are induction of the receptor for advanced glycation end-products (RAGE), modulation of the protein kinase B/atypical protein kinase C zeta, and immune mechanisms.

Obesity

Several studies observed an overall increased death due to cancer as body mass index (BMI) increased above normal range. For example, the Cancer Prevention Study II, at a 16-year follow-up, identified a statistically significant trend for cancer-related mortality as BMI increased from normal to ≥40 for almost all cancers observed.[16] However, the study format did not allow an assessment of how much of it was due to increased incidence, worse prognosis, or worse treatment complications.

The largest body of research on obesity and cancer risk has focused on hormone-dependent cancers, such as breast and prostate cancer. In breast cancer, the relationship is not straightforward. In three separate studies, obesity was associated with a decreased incidence of breast cancer (about 0.6) in young premenopausal women, while the reverse was true for postmenopausal women.[17] Another group at increased risk of breast cancer is composed of women who progressively gain weight during adulthood. In a Swedish study, postmenopausal women who gained 30 kg (66 lbs) or more during adulthood were at twice the risk of having breast cancer compared to women with stable weight.[17] The relationship between obesity and the risk of prostate cancer is more ambiguous. Large cohort studies have explored the role of obesity at different ages. Several observed an association between obesity and a higher risk of prostate cancer. However, others found no or even an inverse association. No consistent age trend is apparent.[18] Obesity has also been associated with an increased risk of colorectal cancer, along with and independently from lower physical activity, diabetes, high calorie intake, and frequent constipation.[4] It does not appear to be associated with an increased risk of NHL.[19]

There are some postulated mechanisms by which obesity might influence cancer risk and prognosis. One is the increased level of leptin, which can act as a growth factor on cancer cells. Other cytokines that might synergize are interleukin (IL)-6, the level of which increases with weight, and IGF-1. The free portion of IGF-1 increases with weight.[17,18,20]

How reversible is the risk associated with obesity? The Iowa Women's Health Study investigators assessed the impact of a weight loss of 20 pounds or more during adulthood, intentional or not.[21] Women who intentionally lost weight and whose weight was back within normal range had an incidence of cancer similar to women with constantly normal body weight. The overall risk reduction was 11% for any cancer (RR 0.89; 95% CI, 0.79–1.00), and highest (19%) for breast cancer (RR 0.81; 95% CI, 0.66–1.00).

Hyperlipidemia

Data on hyperlipidemia and colon cancer are somewhat heterogeneous. In one study, there was a significant positive association between serum cholesterol levels, triglycerides levels, and colorectal carcinoma in situ.[22] In the study of Le Marchand et al,[4] on the other hand, there was an inverse correlation between colon cancer risk and hypercholesterolemia. A high cholesterol diet promotes colon carcinogenesis in rats.[23] Interestingly, there appears to be an interaction between 5-fluorouracil (5-FU) and the lipid metabolism. Patients and animals receiving 5-FU reduced their levels of total cholesterol,[24] and cerivastatin enhanced the cytotoxicity of 5-FU in vitro.[25]

Inflammatory and Autoimmune Diseases

Even in the absence of overt diseases, aging is associated with an increase in several inflammatory markers, such as IL-6, C-reactive protein, and sedimentation rate.[26] Nonspecific markers of autoimmunity, such as

antinuclear antibodies, also tend to increase with age. Does this lead to cancer? Some insight may come from studies with inflammatory and autoimmune diseases, as well as their treatment.

A study analyzed the association of osteoarthritis and rheumatoid arthritis with NHL. It identified no impact of osteoarthritis and an increased risk with rheumatoid arthritis.[27] Another study also found an association of rheumatoid arthritis with NHL (OR 1.5; 95% CI, 1.1–1.9).[28] The risk was most consistent for large-cell B-cell lymphoma. A meta-analysis found a standardized incidence ratio (SIR) of 3.9 (95% CI, 2.5–5.9) for NHL in rheumatoid arthritis.[29] A study examined the association of finger and hand joint and temporomandibular joint prostheses with cancer.[30] It found no association except with NHL in the subgroup that received finger and hand joint replacement for rheumatoid arthritis. The Italian study mentioned above found a significant association of rheumatoid arthritis with both NHL and Hodgkin's disease.[14] A particular presentation of rheumatoid arthritis, Felty's syndrome, shows a strong association with large granular lymphocytosis and leukemia. Rheumatoid arthritis is present in 30% of large granular lymphocyte (LGL) syndromes, and there is a strong association with HLA-DRB1*04.[31] A Scottish study on patients with rheumatoid arthritis and five other rheumatoid conditions found more detailed results.[32] There was an increased risk of death from lung cancer: standardized mortality ratio (SMR) 1.4 (1.2–1.5) in men, 1.6 (1.5–1.8) in women. There was also an increased risk of death from hematopoietic malignancies: men = 1.8 (1.4–2.3), women = 2.0 (1.7–2.3). However, a decreased risk of death from gastrointestinal tract malignancies was seen: men = 0.82 (0.7–1.0), women = 0.8 (0.7–0.9).

A Finnish study comparing the incidence of cancer in patients with celiac disease to that of the general population did not find any difference.[33] However, another study found an increased risk of NHL (OR 2.1; 95% CI, 1.0–4.8).[28]

A well-known association between an autoimmune disease and cancer is Sjögren's disease and lymphoma.[28,29,34] New intriguing data have been published. A study observed many analogies between Sjögren's derived lymphomas and those arising from hepatitis C-related cryoglobulinemia.[35] A direct link with hepatitis C virus (HCV) infection remains yet to be demonstrated. Another study noted that patients with seronegative Sjögren's disease did not develop systemic complications over 10 years, whereas those positive for Ro/La antibodies had a 49.7 relative risk of developing NHL.[36] In a study by Ioannidis et al,[34] patients with a low C4 level or palpable purpura at presentation were at high risk of developing lymphoproliferative disorders.

Several studies addressed the association of systemic lupus erythematosus (SLE) and cancer. In an English clinical database of 276 patients with SLE, there was no increased risk of malignancy compared to expected: standardized incidence rate 1.16 (95% CI, 0.55–2.13). The increase of Hodgkin's disease was trending toward significance: SIR 17.82 (95% CI, 0.45– 99.23).[37] Another study analyzed a Swedish population registry. Again, no overall increased rate of cancer was observed. The standardized morbidity rate for men was 2.24 (95% CI 0.6–5.7) and for women was 1.02 (CI 0.4–2.1). However, some tumors were significantly more frequent: NHL 11.63 (CI 1.4–42.0), lung cancer 5.55 (CI 0.7–20.1), and prostate cancer 6.41 (CI 1.3–18.7).[38] A Danish registry study found again an increased incidence of NHL (RR 5.2; 95% CI, 2.2–10.3).[39] They also found an increased incidence of lung cancer (RR 1.9), liver cancer (RR 8.0), and vagina/vulva cancers (RR 5.7). A more recent Swedish-Danish paper observed an increased risk of NHL (OR 4.6; 95% CI, 1.0–22).[28] The meta-analysis by Zintzaras et al[29] found an SIR for lymphoma of 7.4 (95% CI, 3.3–17). A Canadian study reviewed a clinical cohort of 297 patients with SLE and found an increased risk of cancer (SIR 1.59; 95% CI, 1.05–2.32). The specific sites at risk were cervical cancer: SIR 8.15 (95% CI, 1.63–23.81), and hematopoietic malignancies: SIR 4.9 (95% CI, 1.57–11.43), notably NHL.[40] However, another Canadian study observed no increased risk of cancer (SIR 1.08; 95% CI, 0.70–1.62) except for hematologic malignancies, mostly NHL (SIR 4.1).[41] An American study examining patients from the Chicago Lupus Cohort, which focused on women with SLE,[42] observed an increased incidence of malignancies. The SIR was 2.0 (95% CI, 1.4–2.9) overall. Lung cancer was the only individual cancer significantly increased (SIR 3.1; 95% CI, 1.3–7.9). In Caucasian women, breast cancer was the only significantly increased cancer (SIR 2.9; 95% CI, 1.4–6.4).

The general conclusion that can be drawn from this overview is that whereas the evidence points toward an increase in hematologic malignancies in patients with autoimmune diseases, the evidence is conflicting concerning solid tumors. In general, studies of rheumatologic diseases did not include an assessments of concomitant other diseases.

A key physiopathologic question is whether it is the immune disease itself that increases the risk of malignancy, or its treatment. A study of 128 SLE patients observed that those given intravenous cyclophosphamide were at higher risk of cervical dysplasia ($P<.04$).[43] In the study by Cibere et al,[40] the increased risks of malignancy were independent from the use of cytotoxic agents. A prospective 3-year study in rheumatoid arthritis patients treated with methotrexate found a significant increase in the risk of Hodgkin's disease (SMR 7.4; 95% CI, 3.0–15.3; $P<.001$) but no difference in the general population for NHL (SMR 1.07; 95% CI, 0.6–1.7).[44] These numbers are similar to those men-

tioned in larger rheumatoid arthritis studies discussed above. Of note, however, is that 3 of 8 patients treated with methotrexate withdrawal underwent a remission. These results are consistent with the study by Smedby et al[28] that found no statistically significant correlation with immunosuppressant treatment. Another study found that Epstein-Barr virus (EBV)-associated lymphomas represented only a small fraction of NHL associated with rheumatoid arthritis.[45] A large study showed that patients with inflammatory bowel disease treated with azathioprine did not present an increased risk of cancer compared with their counterparts who did not receive it.[46]

The role of tissue necrosis factor alpha (TNF-α) inhibitors is ambiguous. A case reports study described the early appearance of squamous cell carcinomas of the skin within a few months after starting etanercept therapy for rheumatoid arthritis, even if it postulated that prolonged TNF-α inhibition might have antitumoral effect.[47] A review of the US Food and Drug Administration (FDA) database of patients treated with etanercept or infliximab showed 26 cases of lymphoproliferative disorders, 81% of them lymphomas.[48] The median time between the start of treatment and the development of the lymphoma was again short (median 8 weeks). In two instances, regression was observed on discontinuation of the treatment. In a recent meta-analysis, the relative risk of NHL was not significantly influenced by conventional antirheumatic treatment (SIR 2.5; 95% CI, 0.7–9.0) and cytotoxic treatment (SIR 5.1; 95% CI, 0.9–28.6) but was significantly elevated with biological agents (SIR 11.5; 95% CI, 3.7–26.9).[29] The presently available evidence does not allow definitive conclusions but seems to indicate that increased risks of cancer, if any, appear linked more strongly to the autoimmune disease than to its treatment. A possible exception is anti-TNF-α treatments.

The Other Side of the Coin

Not all diseases of aging are bad. One third of older patients have hypothyroidism. Cristofanilli et al[49] explored the interaction between hypothyroidism and the risk of breast cancer. Using a case control study design, they matched 1,136 women with breast cancer treated at the University of Texas M.D. Anderson Cancer Center with 1,088 healthy participants in a breast cancer screening clinic. The median age was in the early 50s. The prevalence of hypothyroidism was 7% in the breast cancer group and 14.9% in the control group. Their observation was that hypothyroidism (treated or not) was associated with a lesser incidence of breast cancer. Although clearly insufficient to draw firm conclusions, this kind of result warrants further research as most of the comorbidity research has focused on positive risk associations but not on potential protective effects.

There is epidemiologic evidence that allergies and immune-related diagnoses might reduce the risk of glioma and meningioma. In three large cohorts of Swedish patients, Schwartzbaum et al[50] found decreased ratios of gliomas in most cases (HR 0.45; 95% CI, 0.19–1.07, HR 0.45; 95% CI, 0.11–1.92 [high-grade gliomas only, no reduced risk of low-grade gliomas HR 2.60; 95% CI, 0.86–7.81], and HR 0.46; 95% CI, 0.14–1.49). In an American case control study, Brenner et al[51] found that patients with a history of allergies were less likely than controls to have gliomas (OR 0.67; 95% CI, 0.52–0.86), but not meningiomas or acoustic neuromas. Patients with autoimmune diseases (including diabetes) were less likely to have gliomas (OR 0.49; 95% CI, 0.35– 0.69), or meningiomas (OR 0.59; 95% CI, 0.38–0.92).

Nonsteroidal Anti-Inflammatory Drugs and Statins

Much has been written about the potential protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) and statins. The tumor in which the role of NSAIDs is the most studied is colorectal cancer. There is substantial epidemiological evidence that the regular use of aspirin, other NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, and aminosalicylates is associated with about a 50% decreased incidence of colon cancer.[52-54] The effect appears dose-dependent.[55] Several randomized studies have been published in which the occurrence of adenomas is often used as a surrogate end point, given the orderly progression of colorectal neoplasms. An American Intergroup study randomized 635 colorectal cancer patients to aspirin 325 mg/day or placebo.[56] Patients underwent at least one colonoscopy at a median of 12.8 months after randomization. Adenomas were found in 17% of the aspirin group and 27% of the control group (P=.004). The mean number of adenomas was also decreased. The time to detection of first adenoma was increased in the aspirin group (HR 0.64; 95% CI, 0.43–0.94, P=.022). This study targeted patients with a low risk of cancer recurrence, and patients with familial adenomatous polyposis or inflammatory bowel disease were excluded. Another study, again in patients without familial risk syndromes, randomized 1,121 patients with colorectal adenomas to placebo, aspirin 81 mg/day, or aspirin 325 mg/day.[57] On control colonoscopy at least 1 year after randomization, the incidence of adenomas was 47% in the control group, 38% in the 81-mg group, and 45% in the 325-mg group. The RR was 0.81 (95% CI, 0.69–0.96) in the 81-mg group and 0.96 (95% CI, 0.81–1.13) in the 325-mg group compared to placebo. Another study in patients with colorectal adenomas randomized 272 patients to lysine acetylsalicylate 160 or 300 mg/day or placebo.[58] After 1 year, the incidence of

adenoma was 30% in the aspirin group and 41% in the placebo group (RR 0.73; 95% CI, 0.52–1.04; *P*=.08). On stepwise regression, treatment with aspirin had a significant impact (*P*=.01). One study attempted to reduce already present polyps in patients with familial adenomatous polyposis (FAP).[59] Patients were randomized to placebo or to celecoxib 100 or 400 mg twice daily. The patients receiving 400 mg of celecoxib had a 28% reduction in the number of polyps (*P*=.003) and a 30.7% reduction in the sum of polyp diameters (*P*=.001) compared with a reduction of 4.5% and 4.9%, respectively, in the placebo group. In the group receiving 100 mg of celecoxib, the reductions were 11.9% (*P*=.33), and 14.6% (*P*=.09). The same authors also looked at the decrease of duodenal polyps in these patients[60] and found a 14.5% decrease after 6 months of celecoxib 400 mg b.i.d. compared with 1.4% for placebo (*P*=.436). Again, the results obtained with 100 mg b.i.d. of celecoxib were intermediate. A third study addressed patients with FAP.[61] They were randomized to sulindac 75 or 150 mg twice daily or placebo. After 4 years of treatment, adenomas developed in 43% of the treated subjects vs 55% of the placebo group (*P*=.54).

The impact of NSAID use on the incidence of breast cancer was also analyzed. A meta-analysis of 14 studies found an 18% risk reduction, comparable for aspirin and other NSAIDs.[62] A study on the Women's Health Initiative cohort, focusing on 80,741 postmenopausal women between 50 and 79 years of age, observed a 21% reduction for 5 to 9 years of regular NSAIDs and a 28% reduction for 10 or more years.[63] The effect was more pronounced for ibuprofen (49%) than for aspirin (21%). In a single institution case control series, COX-2 inhibitors, regular aspirin, and ibuprofen or naproxen reduced the risk of breast cancer by about half, whereas acetaminophen and low-dose aspirin did not.[64]

A recent meta-analysis reviewed the effect of NSAIDs on other solid tumors.[52] In addition to breast cancer, reviewed above, a decreased risk was found for cancer of the esophagus, stomach, ovary, prostate, and lung. No significant effect was found for pancreas, kidney, and bladder cancer (Table). However, another meta-analysis did not support these results for ovarian cancer.[65]

By contrast, Cerhan et al,[27] using SEER data, recently showed an association between the use of NSAIDs and an increased incidence of lymphoma. The incidence of NHL increased about twofold in patients taking aspirin, other NSAIDs, or both. The authors corrected for a history of osteoarthritis or rheumatoid arthritis. Although rheumatoid arthritis was associated with an increased risk of NHL, the association of aspirin with NHL was independent of arthritis history. These data are highly consistent with studies of rheumatoid arthritis in which patients were found to have a decreased risk of colon cancer and an increased risk of NHL.[27] Other series, however, did not find a similar association, and a case control study found a protective effect of NSAIDs on NHL.[27] A Swedish population study found a marginal increase of NHL in NSAIDs users.[66] That study also observed an association with multiple uses of antibiotics. However, the data on medication use and the risk of NHL are heterogeneous, as reviewed by the authors, and in the absence of primary comorbidity data difficult to separate from the effect of the underlying comorbidity. As a general rule, studies on the use of NSAIDs provide little data on the patients' comorbidities, whether related or not to the need for NSAIDs, and this might explain some of heterogeneities. For example, a 2-week course of high-dose aspirin (about 7g/day) was demonstrated to decrease fasting plasma glucose, plasma cholesterol, and triglyc-

Table. — Overall Relative Risk and 95% Confidence Interval According to Cancer Site and Type of Exposure

	No. of Studies	NSAIDs RR (95% CI)	No. of Studies	Aspirin RR (95% CI)	No. of Studies	Non-aspirin NSAIDs RR (95% CI)
Esophagus	4	0.65 (0.46–0.92)	4	0.51 (0.38–0.69)		
Stomach	3	0.54 (0.39–0.75)	5	0.73 (0.63–0.84)	2	0.91 (0.66–1.25)
Pancreas	2	1.09 (0.59–2.01)	3	0.69 (0.40–1.20)		
Breast	9	0.77* (0.66–0.88)	11	0.77 (0.69–0.86)	5	0.86 (0.73–1.00)
Ovary	6	0.74 (0.61–0.90)	6	0.91 (0.79–1.06)		
Prostate	4	0.64* (0.34–1.21)	7	0.92 (0.81–1.05)	2	0.84 (0.68–1.05)
Kidney			6	1.23* (0.86–1.75)		
Bladder	3	0.91 (0.71–1.18)	3	0.91 (0.73–1.13)		
Lung	3	0.65* (0.34–1.22)	5	0.84* (0.66–1.07)		

* *P*<.05 (heterogeneity test).

From González-Pérez A, García Rodríguez LA, López-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer*. 2003;3:28.

erides, and insulin clearance in 9 subjects with type 2 diabetes, probably by interacting with IKKβ.[67] Therefore the impact of NSAIDs might be multifactorial.

Some studies report that statins decrease the risk of cancer[68-70] or have no effect on the risk of cancer.[71-75] A recent meta-analysis reviewed 26 randomized trials of statins for the incidence of cancers.[76] Statins did not reduce the incidence of cancer (OR 1.02; 95% CI, 0.97–1.07) or cancer deaths (OR 1.01; 95% CI, 0.93–1.09). There were no significant subgroup effects, either by cancer type or by statin type. Another meta-analysis focusing on breast cancer did not find a significant effect.[77] Further exploration is needed before the impact of statins on cancer can be fully understood.

Comorbidity and Cancer Prognosis

Several investigators have attempted to determine if there is a relationship between comorbidity and cancer prognosis. Many studies, such as the pioneering report in 1987 by Greenfield et al,[78] found that comorbidity modifies the treatment of older cancer patients. Numerous reports, notably epidemiologic studies, observed that comorbidity affected both treatment and prognosis, making it difficult to separate the respective contributions of comorbidity, functional status, and treatment reduction to the prognosis.

What data are available on the direct impact of comorbidity on the outcome of the cancer itself? A well-controlled study by Meyerhardt et al[79] analyzed the population of an intergroup adjuvant trial in colon cancer and observed that diabetes was associated with a shorter disease-free survival (Figure). The intensity of treatment was the same in diabetic and nondiabetic patients and thus could not explain the 11% absolute difference in 5-year disease-free survival (also associated with a similar difference in recurrence-free and overall survival). This finding suggests a true biologic interaction between diabetes and colon cancer. In another study focusing on patients undergoing resection of hepatic colorectal cancer metastasis,[80] diabetic patients had a higher perioperative mortality (8% vs 2%, $P<.02$) but no difference in long-term survival.

In the study cohort mentioned above, Meyerhardt et al[81] also analyzed the impact of obesity on outcome.

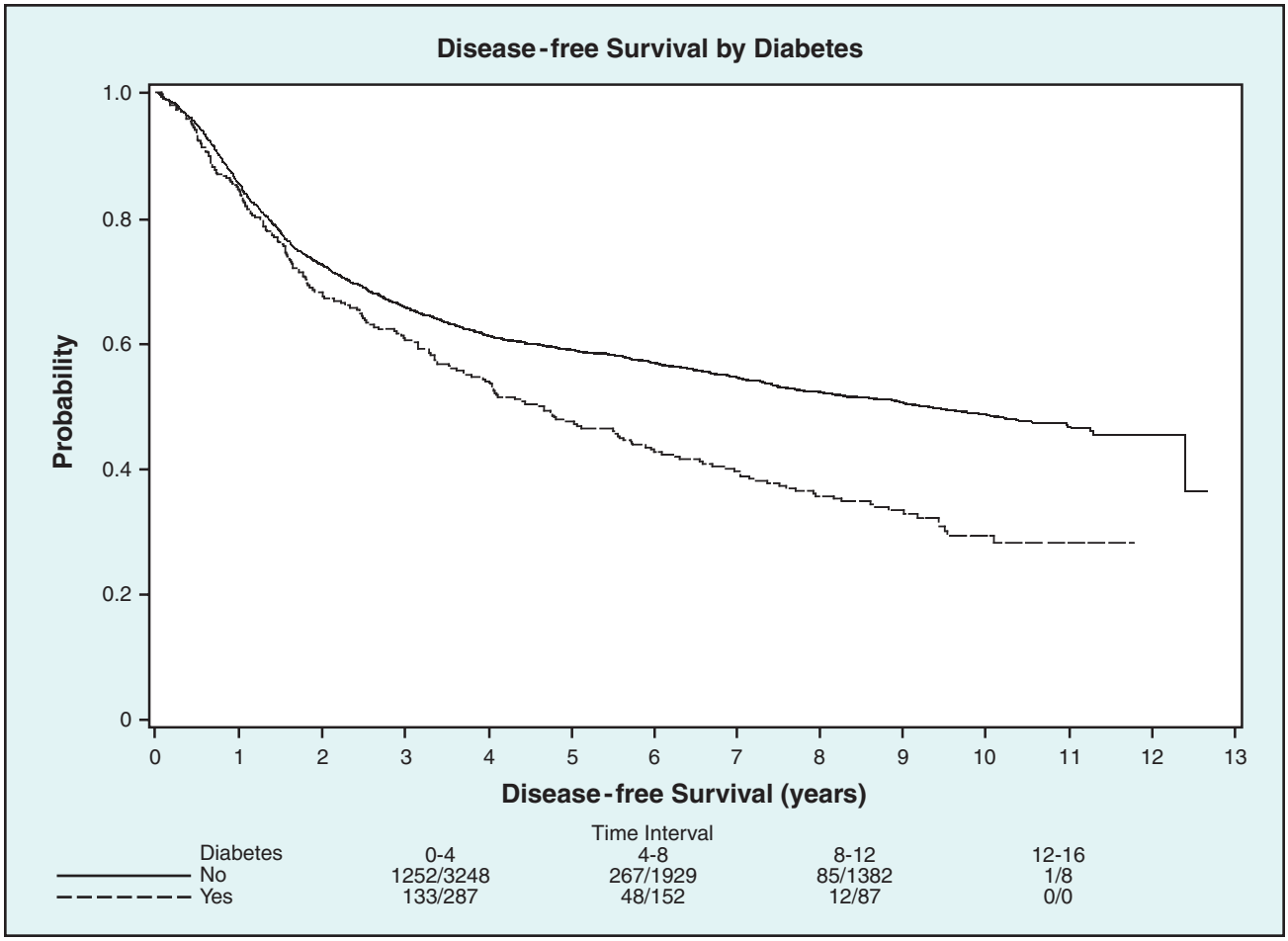

Figure. — Effect of diabetes on disease-free survival in an intergroup adjuvant trial in colon cancer. From Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. *J Clin Oncol.* 2003;21:433-440. Reprinted with permission from the American Society of Clinical Oncology.

Again, no differences in treatment intensity were observed. Obese women (BMI ≥ 30 kg/m^2) had a higher mortality risk (HR 1.34; 95% CI, 1.07–1.67) and a nonsignificant increase in disease recurrence (HR 1.24; 95% CI, 0.98–1.59). No differences were seen in men. A recent single-institution study analyzed retrospectively the effect of obesity on advanced ovarian cancer (stage III–IV).[20] Optimal debulking was achieved at a similar high rate in obese and normal weight women. They typically received 6 to 7 cycles of chemotherapy, and only 6 patients could not complete the chemotherapy, without correlation with BMI. Progression-free survival was 32, 24, 18, and 21 months for underweight, normal weight, overweight, and obese patients, respectively (*P*=.02). The corresponding figures for overall survival were as follows: not reached, 70, 79, and 33 months, respectively (*P*=.02). Obesity also appears to affect the prognosis of prostate cancer independently from treatment. It is associated with a higher rate of positive margins after radical prostatectomy. However, even among patients with negative margins, the rate of prostate-specific antigen (PSA) relapse is higher among obese men.[18] One study analyzed PSA relapse after brachytherapy. The authors did not observe a correlation with BMI at 8 years.[82] Several cohort studies reported an association of high BMI with worse prognosis of breast cancer. Some of these cohort studies adjusted for treatment and supported a persisting independent association of BMI with prognosis. There is some heterogeneity in the results as to whether this pertains to all breast cancer patients or whether the effect is higher in certain subgroups (eg, estrogen-receptor–negative patients).[17,83]

Hyperinsulinemia is associated with a worse disease-specific survival in prostate cancer,[84] as well as in colon cancer[79] and breast cancer.[85] Hammarsten and Högstedt[84] published the results of a prospective cohort of 320 patients diagnosed with T2 and T3 prostate cancer between 1995 and 2003. Mean patient age was in the early 70s. Several conditions included in most definitions of the metabolic syndrome (or insulin-resistance syndrome) were associated with the prostate cancer-specific survival. Survival was worse as the number of metabolic disorders increased (*P*=.018). Given the high prevalence of metabolic syndrome in the elderly inhabitants of developed countries (40%–45% prevalence in the US population after 60 years of age[86]), this is a highly relevant problem when trying to improve the survival of older cancer patients. On the other hand, a community database study named Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) did not reveal an association of diabetes with prostate cancer aggressiveness at diagnosis or risk of recurrence.[87]

Conversely, according to a recent study, NHL in patients with rheumatoid arthritis might have a better prognosis compared with control subjects, although the interpretation of the results is complicated by potential competing causes of mortality.[88]

Information is limited regarding the reversibility of these prognostic factors. A randomized, blinded study analyzed the effect of rosiglitazone in 106 men with prostate cancer. The study hypothesized that rosiglitazone would decrease the recurrence of prostate cancer through its role as a peroxisome proliferator-activated receptor γ (PPAR γ) agonist. It failed to demonstrate an increase in the PSA doubling time. However, the study was small and excluded patients treated for diabetes.[89]

Conclusions

Comorbidity and its treatment appear to exert a significant effect on the behavior of cancer in older patients. Rather than a blanket effect, this impact might be attached to groups of syndromes with common pathophysiologic mechanisms. In addition to paying attention to the impact of cancer treatment on comorbidity or on the effect of comorbidity in delivering cancer treatment, our future endeavors will need to consider the direct impact of comorbidity on the risk and the behavior of the cancer in elderly patients.

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