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REVIEW

The impact of comorbidity on cancer survival: a review

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Background: A number of studies have shown poorer survival among cancer patients with comorbidity. Several mechanisms may underlie this finding. In this review we summarize the current literature on the association between patient comorbidity and cancer prognosis. Prognostic factors examined include tumor biology, diagnosis, treatment, clinical quality, and adherence.

Methods: All English-language articles published during 2002–2012 on the association between comorbidity and survival among patients with colon cancer, breast cancer, and lung cancer were identified from PubMed, MEDLINE and Embase. Titles and abstracts were reviewed to identify eligible studies and their main results were then extracted.

Results: Our search yielded more than 2,500 articles related to comorbidity and cancer, but few investigated the prognostic impact of comorbidity as a primary aim. Most studies found that cancer patients with comorbidity had poorer survival than those without comorbidity, with 5-year mortality hazard ratios ranging from 1.1 to 5.8. Few studies examined the influence of specific chronic conditions. In general, comorbidity does not appear to be associated with more aggressive types of cancer or other differences in tumor biology. Presence of specific severe comorbidities or psychiatric disorders were found to be associated with delayed cancer diagnosis in some studies, while chronic diseases requiring regular medical visits were associated with earlier cancer detection in others. Another finding was that patients with comorbidity do not receive standard cancer treatments such as surgery, chemotherapy, and radiation therapy as often as patients without comorbidity, and their chance of completing a course of cancer treatment is lower. Postoperative complications and mortality are higher in patients with comorbidity. It is unclear from the literature whether the apparent undertreatment reflects appropriate consideration of greater toxicity risk, poorer clinical quality, patient preferences, or poor adherence among patients with comorbidity.

Conclusion: Despite increasing recognition of the importance of comorbid illnesses among cancer patients, major challenges remain. Both treatment effectiveness and compliance appear compromised among cancer patients with comorbidity. Data on clinical quality is limited.

Keywords: comorbidity, cancer, diagnosis, treatment, survival

Introduction

It is essential to personalized medicine to understand how patient characteristics such as age and coexisting diseases (comorbidity) affect cancer detection, treatment, and outcome. With more than 60% of cancer patients diagnosed at age 65 or older in high-income countries,[1] many patients have comorbidities that complicate the decision-making process. Because the elderly and persons with comorbidity are often underrepresented in clinical trials,[2,3] information regarding treatment effectiveness is

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often extrapolated from studies of younger patients without comorbidity.

Several studies have shown poorer survival among cancer patients with comorbidity,[4–11] but the underlying mechanisms remain unclear. In recent decades 5-year survival rates have improved among cancer patients without comorbidity, but not among patients with severe comorbidity.[4–6] An understanding of how comorbidity affects survival in patients with cancer is needed to guide clinical practice. We therefore reviewed the literature on the association between comorbidity and survival among patients with three of the most commonly diagnosed cancers: colon cancer, breast cancer, and lung cancer.

Methods

Definition and measurement of comorbidity

Comorbidity has been defined as "any additional clinical entity that has existed or that may occur during the clinical course of a patient with an index disease under study."[12,13] The term "multimorbidity" is often used interchangeably with "comorbidity" but has a slightly different meaning. Multimorbidity refers to the coexistence of ≥2 illnesses without identifying an index disease.[14] Comorbidity must also be distinguished from complications that arise as a consequence of the cancer or its treatment. A number of studies have examined the prognostic impact of patients' "performance status" at the time of cancer diagnosis. Performance status is a measure of a cancer patient's well-being defined as the amount of normal daily activity the patient can maintain.[15–17] However, performance status is affected by cancer, complications of cancer, and comorbid conditions.[18] Therefore, measures of comorbidity must be distinguished from measures of performance status.

Data on comorbid diseases are available from different data sources, such as medical records, administrative databases, physical examinations, and self-reports using questionnaires.[19–21] Comorbidity can be assessed by counting the number of coexisting diseases diagnosed in a cancer patient or by using a comorbidity index that combines the number and severity of the diseases. The most widely used index is the Charlson Comorbidity Index (CCI). The original Charlson measure was constructed to predict 1-year mortality in 559 medical patients as well as 10-year mortality rates for death attributable to comorbid diseases among 685 breast cancer patients.[22] The index is based on 19 distinct medical disease categories. Each condition has a weight assigned from 1 to 6, derived from the relative risk estimates obtained from a regression model. The CCI score is the sum of weights for all prevalent conditions. The score can theoretically range from 0–33 but was collapsed into categories of 0, 1–2, 3–4, and ≥5 in its initial presentation.[22,23]

Literature search

We searched PubMed, MEDLINE and Embase to identify and summarize existing information on the association between comorbidity and cancer survival in patients with colon cancer, breast cancer, and lung cancer. We used the following keywords to identify potentially useful articles: "comorbidity," "multimorbidity," and "coexisting diseases." In addition, we searched for articles on the following prevalent comorbid diseases: diabetes, cardiovascular diseases, chronic pulmonary disease, and dementia. Furthermore, we queried the databases using the terms "colon cancer," "breast cancer," "lung cancer," and "comorbidity" combined with such terms as "pathogenesis," "histology," "differentiation," "stage," "diagnosis," "centralized treatment," "specialized treatment," "patient volume," and "surgeon volume." We limited our search to English-language articles published within the last 10 years. All searches were performed at the end of November 2012. Our PubMed search strategy is described in detail in Table S1.

Overall, we identified 2,692 potentially eligible articles (Figure 1). The first author (MS) reviewed the titles and abstracts and removed articles not relevant to comorbidity and cancer survival. The information summarized in this review was gleaned from the remaining articles and prior publications cited by these articles.

Results

Prevalence of comorbidity among cancer patients

As shown in Table 1, comorbidity is common in patients with colon cancer (14%–68%), breast cancer (20%–35%), and lung cancer (26%–81%). A recent Danish population-based cohort study found that elderly patients with colorectal and lung cancer had a higher prevalence of comorbidity than an age- and sex-matched comparison cohort from the general population, as measured by CCI scores (CCI score of 1 or 2: 12.3% vs 9.6% and CCI score of ≥3: 5.6% vs 4.0%).[24] The probable reason for these findings is that known risk factors for colorectal or lung cancer, such as smoking, obesity, and physical inactivity, are also common risk factors for non-cancer diseases such as ischemic heart disease.

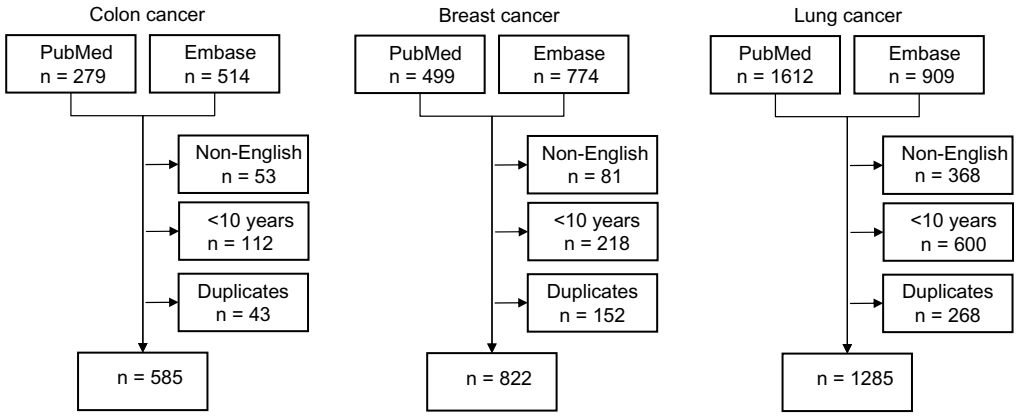

Figure 1 Flowchart of the studies retrieved from the PubMed, MEDLINE and Embase literature search.

As average life expectancy increases in Western countries, the proportion of elderly cancer patients also is expected to increase.[25] Because the prevalence of comorbidity increases with age, the number of cancer patients with comorbidity will increase concomitantly. This is indicated in a US study of 49,646 women aged 67 years or older with breast cancer in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data set. Among these patients, 23% of women aged 85–89 years and 11.2% of women aged 67–69 years had severe comorbidity.[26] In a study from The Netherlands, 53% of patients aged 60–74 years were found to have at least one comorbidity, and this proportion increased to 63% in patients aged 75 years and older.[24]

Impact of comorbidity on cancer survival

Most observational studies have found that cancer patients with comorbidities have poorer survival than patients without comorbidities.[4–11,24,28–30] Cohort studies with 5–7 years of follow-up have reported 1.1- to 5.8-fold higher mortality for breast cancer patients with any comorbidity compared to patients with no comorbidity.[4,20,26,31,32] Similarly, studies of patients with colon cancer have reported 1.2- to 4.8-fold higher 5-year mortality for patients with comorbidity versus without comorbidity.[5,8,9,25,32,34] Correspondingly, mortality in patients with lung cancer is 1.1 to 1.5 times higher for patients with comorbidity in studies with 1–5 years of follow-up.[7,29,34,35] Not surprisingly, if survival among patients with a particular type of cancer is generally very poor, the additional effect of comorbid diseases on mortality on a relative scale is small.[34,36,37] Thus, the relatively lower prognostic impact of comorbidity among lung cancer patients is probably due to a 1-year mortality rate above 70% even among otherwise healthy patients.[24]

Stage at diagnosis influences decisions about the appropriate course of treatment and is strongly associated with cancer survival. Thus, stage-specific analyses may provide more insight into the association between comorbidity and cancer survival. Among 62,591 women diagnosed with early-stage breast cancer in Denmark during 1990–2008, the adjusted hazard ratios (HRs) for all-cause mortality were 1.45 (95% confidence interval [CI]: 1.40–1.51) for patients with low comorbidity, 1.52 (95% CI: 1.45–1.60) for patients with moderate comorbidity, and 2.21 (95% CI: 2.08–2.35) for patients with severe comorbidity, compared to patients without comorbidity. Median follow-up time was 8.2 years.[6] Recently, Patnaik et al[28] used the SEER-Medicare linked data set to determine the effect of 13 distinct comorbid conditions on survival and all-cause mortality among 64,034 breast cancer patients aged 66 years or older from 1992 to 2000. Patients with any of the 13 comorbidities had lower rates of 5-year survival than patients with no comorbidities. In addition, stage I cancer patients with serious comorbid conditions had survival rates similar to stage II cancer patients without comorbidities. Thus, patients with early-stage cancers and significant comorbidities had outcomes comparable to patients with later-stage tumors.

A key question is whether the higher mortality observed in cancer patients with comorbidity stems from their comorbidity or whether their cancer-specific mortality is elevated. In a recent Danish cohort study of 6,325 patients aged ≥70 years with breast, lung, colorectal, prostate, or ovarian cancer, 5-year all-cause mortality increased with higher levels of comorbidity.[24] For 5-year cancer-specific mortality, however, comorbidity was associated with increased rates only in patients with lung cancer (5-year HR for CCI score ≥3 vs CCI score of 0 = 1.29 [95% CI: 1.03–1.60]).

Table 1 Results of selected studies on the association between comorbidity and treatment

Author	Design, country	Study duration	No of patients	Study population	Comorbidity assessed	% with comorbidity
Colon cancer						
Hu et al[102]	Cohort study, USA	1991–2005	12,265	CC, ≥65 years, stage III	CCI[22]	Overall: 47.8% CCI 1: 28.1% CCI≥2: 19.6%
Kennedy et al[89]	Cohort study, USA	2005–2008	5,914	CC, ≥65 years, stage III	List of individual diseases BMI ASA score	N/A
Morris et al[91]	Population-based cohort study, UK	1998–2006	162,920	CRC, all stages	CCI	Overall: 14.1% CCI 1: 8.4% CCI 2: 4.0% CCI≥3: 1.7%
van Steenbergen et al[93]	Population-based cohort study, The Netherlands	2001–2007	1,637	CC, stage III	CCI	Overall: 51.2% CCI 1: 28.3% CCI≥2: 22.8%
Winget et al[105]	Population-based cross-sectional study, Canada		772	Surgically treated CC, stage III	CCI	Overall: 32%
Bradley et al[94]	Cohort study, USA	1997–2000	4,765	CC patients who underwent resection, all stages	CCI	Overall: 34.2% CCI 1: 21.4% CCI≥2: 12.7%
Lemmens et al[138]	Cohort study, The Netherlands	1995–1999	279	CC patients who underwent resection, stage I–III	CCI	Overall: 68% CCI 1: 31% CCI≥2:37%

End points assessed	Results related to comorbidity	Main conclusion
Chemotherapy initiation and completion	Adj ORs of chemotherapy initiation compared with those with CCI = 0: CCI 1: 0.63 (95% CI: 0.57–0.70) CCI≥2: 0.37 (95% CI: 0.33–0.42) Adj ORs of chemotherapy completion compared to those with CCI = 0: CCI 1: 0.87 (95% CI: 0.75–1.01) CCI≥2: 0.63 (95% CI: 0.52–0.75)	Patients with comorbidity are less likely to initiate and complete chemotherapy.
Risk of surgical complication 30-day postoperative mortality	Adj OR of postoperative complications BMI<18: 0.91 (95% CI: 0.62–1.34) BMI 25–29.9: 1.22 (95% CI: 1.04–1.43) BMI 30–49: 1.26 (95% CI: 1.05–1.49) COPD: 1.84 (95% CI: 1.49–2.27) ASA2 (severe): 1.29 (95% CI: 1.10–1.52) ASA3 (life threatening): 1.65 (95% CI: 1.26–2.16) Adj ORs of 30-day postoperative mortality: ASA2 (severe): 1.59 (95% CI: 0.98–2.58) ASA3 (life threatening): 2.58 (95% CI: 1.41–4.72)	Patients with comorbidity and obesity are more likely to experience complications after surgery. Short-term mortality after surgery is higher among patients with comorbidity.
30-day postoperative mortality	Adj ORs of death within 30 days of surgery compared to those with CCI = 0: CCI 1: 2.12 (95% CI: 1.99–2.26) CCI 2: 2.46 (95% CI: 2.26–2.68) CCI≥3: 4.51 (95% CI: 4.06–5.01)	Short-term mortality after surgery is higher among patients with comorbidity.
Receipt of chemotherapy	Adj ORs of receiving chemotherapy compared to those with CCI = 0: CCI 1: 0.7 (95% CI: 0.5–0.9) CCI≥2: 0.4 (95% CI: 0.3–0.6)	Patients with comorbidity are less likely to receive chemotherapy.
Consultation with medical oncologist within 6 months of diagnosis Receipt of standard treatment	36% of patients with CCI ≥ 1 did not consult an oncologist vs 12% of patients with CCI = 0. Adj RR was 1.61 (95% CI: 1.24–2.09) for not having a consultation and 1.55 (95% CI: 1.31–1.83) for not receiving guideline-recommended treatment, compared to patients with CCI = 0.	Patients with comorbidity are less likely to be referred to a medical oncologist and to receive treatment consistent with guidelines.
Adjuvant chemotherapy initiation, completion, and evaluation by oncologist	Adj ORs of chemotherapy initiation compared to those with CCI = 0: CCI 1: 0.83 (95% CI: 0.70–1.04) CCI≥2: 0.62 (95% CI: 0.49–0.78) Adj ORs of chemotherapy completion compared to those with CCI 0: CCI 1: 1.06 (95% CI: 0.77–1.44) CCI≥2: 0.58 (95% CI: 0.38–1.61) Adj ORs of oncology evaluation compared to those with CCI=0: CCI 1: 1.25 (95% CI: 0.98–1.59) CCI≥2: 1.61 (95% CI: 1.17–2.20)	Patients with comorbidity are less likely to initiate and complete chemotherapy, but more likely to be evaluated by an oncologist.
Risk of surgical complication	Adj ORs of surgical complications compared with patients with CCI=0: Any comorbidity: 1.1 (95% CI: 0.91–1.4) Previous malignancy: 1.2 (95% CI: 0.7–2.1) CVD: 0.9 (95% CI: 0.5–1.5) COPD: 1.8 (95% CI: 0.7–4.7) Diabetes: 0.6 (95% CI: 0.1–1.4) Hypertension: 0.7 (95% CI: 0.4–1.4) DVT: 9.0 (95% CI: 1.1–27.9)	Odds of complications are higher among patients with COPD and DVT, but not among those with previous malignancy, CVD, diabetes, and hypertension.

(*Continued*)

Table 1 (*Continued*)

Author	Design, country	Study duration	No of patients	Study population	Comorbidity assessed	% with comorbidity
Luo et al[95]	Cohort study, USA	1992–1999	7,569	CC, 66–99 years, stage III	CCI	Overall: 32.3% CCI 1: 20.5% CCI 2: 7.4% CCI≥3: 4.4%
Neugut et al[129]	Population-based cohort study, USA	1995–1999	3,733	CC, ≥65 years, stage III	CCI	Overall: 51.7% CCI 1: 29.5% CCI>1: 22.2%
Gross et al[108]	Cohort study, USA	1993–1999	5,330	CC, ≥65 years, stage III	List of individual diseases	CHF: 16.0% Diabetes: 17.8% COPD: 18.8% Liver disease: 1.1% Myocardial infarction: 7.4%
Breast cancer						
Berglund et al[38]	Population-based cohort study, Sweden	1992–2008	42,646	BC, all stages	CCI	Total: 13% CCI 1: 7% CCI≥2: 6%

End points assessed	Results related to comorbidity	Main conclusion
Referral to medical oncologist within 6 months of diagnosis Receipt of chemotherapy	Adj RRs of referral compared to those with CCI=0: CCI 1: 1.02 (95% CI: 0.99–1.04) CCI 2: 1.00 (95% CI: 0.96–1.05) CCI≥3: 0.87 (95% CI: 0.81–0.93) Adj RRs for receipt of chemotherapy, all patients compared to those with CCI=0: CCI 1: 0.92 (95% CI: 0.88–0.96) CCI 2: 0.86 (95% CI: 0.80–0.93) CCI≥3: 0.74 (95% CI: 0.66–0.84) Adj RRs for receipt of chemotherapy among patients referred to oncologist compared to those with CCI=0: CCI 1: 0.92 (95% CI: 0.89–0.96) CCI 2: 0.85 (95% CI: 0.80–0.92) CCI≥3: 0.71 (95% CI: 0.63–0.80)	Comorbidity decreases the likelihood of receiving chemotherapy, but does not affect referral to a medical oncologist.
5–7 months of fluorouracil-based adjuvant chemotherapy	Adj ORs for 5–7 months' treatment compared to those with CCI=0: CCI 1: 0.75 (95% CI: 0.60–0.97) CCI>1: 0.62 (95% CI: 0.46–0.84)	Patients with comorbidity are less likely to complete 5–7 months of fluorouracil-based chemotherapy.
Initiation of chemotherapy Completion of chemotherapy if initiated Hospitalization attributable to chemotherapy among treated patients	Adj ORs of chemotherapy initiation compared with patients without condition: CHF: 0.49 (95% CI: 0.40–0.60) COPD: 0.83 (95% CI: 0.70–0.99) Diabetes: 0.81 (95% CI: 0.68–0.97) Adj ORs of chemotherapy completion compared with patients without condition: CHF: 0.79 (95% CI: 0.60–1.06) COPD: 0.80 (95% CI: 0.65–1.00) Diabetes: 0.86 (95% CI: 0.69–1.07) Adj ORs for hospitalizations attributable to chemotherapy (treated vs untreated): –CHF: 1.92 (95% CI: 1.60–2.30) +CHF: 1.20 (95% CI: 0.82–1.73) –COPD: 1.78 (95% CI: 1.49–2.14) +COPD: 1.61 (95% CI: 1.13–2.27) –Diabetes: 1.80 (95% CI: 1.51–2.16) +Diabetes: 1.67 (95% CI: 1.16–2.41)	Patients with CHF, COPD, and diabetes are less likely to receive and complete chemotherapy. However, the odds of hospitalizations attributable to chemotherapy are higher among patients without CHF, COPD, and diabetes.
Treatment received	Adj ORs compared to those with CCI=0: No surgery CCI 1: 1.88 (95% CI: 1.65–2.14) CCI≥2: 3.01 (95% CI: 2.67–3.41) Mastectomy CCI 1: 1.01 (95% CI: 0.93–1.09) CCI≥2: 0.97 (95% CI: 0.89–1.05) BCS CCI 1: 0.81 (95% CI: 0.74–0.88) CCI≥2: 0.63 (95% CI: 0.58–0.69) BCS+RT CCI 1: 0.89 (95% CI: 0.78–1.02) CCI≥2: 0.72 (95% CI: 0.62–0.83) Tamoxifen CCI 1: 0.93 (95% CI: 0.84–1.04) CCI≥2: 0.88 (95% CI: 0.78–0.99)	Patients with comorbidity are less likely to undergo surgery and to receive BCS, chemotherapy, and tamoxifen.

(*Continued*)

Table 1 (*Continued*)

Author	Design, country	Study duration	No of patients	Study population	Comorbidity assessed	% with comorbidity
Land et al[6]	Population-based cohort study, Denmark	1990–2008	62,591	BC	CCI	Overall: 19.7% CCI 1: 10.2% CCI 2: 6.0% CCI≥3: 3.5%
O'Connor et al[100]	Cohort study, USA	1997–2004	204	≥65 years, stage I–III	CCI BMI	N/A
Punglia et al[106]	Cohort study, USA	1991–2002	18,050	≥65 years who received BCS and RT, stage 0–II breast cancer	CCI	Overall: 23.3% CCI 1: 17.4% CCI 2: 3.2% CCI≥3: 2.6%
Gold et al[104]	Cohort study, USA	1991–1999	7,791	DCIS + stage I breast cancer	Klabunde inpatient and outpatient comorbidity indices[149]	N/A
Yood et al[139]	Cohort study, USA	1990–1994	1,837	≥65 years, stage I–II	CCI	Overall: 31.8% CCI 1: 27.1% CCI≥2: 4.7%
Giordano et al[140]	Cohort study, USA	1991–1999	41,390	≥65 years, stage I–III	CCI	Overall: 35.0% CCI 1: 24.6% CCI≥2:10.4%
Buist et al[141]	Cohort study, USA	1990–1994	897	≥65 years, stage I–IIB	BMI CCI + list of individual diseases	64% were overweight or obese

End points assessed	Results related to comorbidity	Main conclusion
	Aromatase inhibitor CCI 1: 1.17 (95% CI: 0.99–1.39) CCI≥2: 1.34 (95% CI: 1.12–1.60) Chemotherapy CCI 1: 0.78 (95% CI: 0.68–0.89) CCI≥2: 0.76 (95% CI: 0.66–0.87)	
Treatment received Mortality	Mastectomy 63% in CCI 0 vs 63% in CCI≥3 Lumpectomy 33% in CCI 0 vs 22% in CCI≥3 Biopsy alone 4% in CCI 0 vs 15% in CCI≥3 Adjuvant therapy None: 25% in CCI 0 vs 13% in CCI≥3 Endocrine therapy 26% in CCI 0 vs 23% in CCI≥3 Chemotherapy 15% in CCI 0 vs 6% in CCI≥3 Chemotherapy + endocrine therapy 10% in CCI 0 vs 2% in CCI≥3 Unknown 24% in CCI 0 vs 56% in CCI≥3 CCI≥3 women had fewer lymph nodes removed	Patients with comorbidity are more likely to receive BCS without radiation therapy, to undergo only biopsy, and to receive less adjuvant therapy.
Problematic chemotherapy delivery	Reduced dose of chemotherapy: CCI≥1 vs CCI 0: Adj OR 0.97 (95% CI: 0.34–2.73) BMI≥30 vs BMI<30: Adj OR 1.84 (95% CI: 0.48–7.10) Hypertension yes vs no: Adj OR 1.86 (95% CI: 0.61–5.72) Unplanned delay in chemotherapy: CCI≥1 vs CCI 0: Adj OR 2.55 (95% CI: 1.10–5.89) BMI≥30 vs BMI<30: Adj OR 1.66 (95% CI: 0.56–4.88) Hypertension yes vs no: Adj OR 2.51 (95% CI: 1.02–6.20) Incomplete chemotherapy CCI≥1 vs CCI 0: Adj OR 1.97 (95% CI: 0.88–4.41) BMI≥30 vs BMI<30: Adj OR 2.19 (95% CI: 0.79–6.09) Hypertension yes vs no: Adj OR 1.64 (95% CI: 0.72–3.74)	Patients with comorbidity and obesity are more likely to receive a reduced dose of chemotherapy, to experience unplanned delays in treatment initiation, and to receive less than a complete course of chemotherapy.
Interval to RT of over 6 weeks	Adj ORs compared to those with CCI=0: CCI 1: Adj OR 1.11 (95% CI: 1.02–1.21) CCI 2: Adj OR 1.12 (95% CI: 0.93–1.33) CCI≥3: Adj OR 0.89 (95% CI: 0.72–1.09)	Patients with low or moderate but not severe comorbidity are more likely to experience delays in RT initiation.
Delay and noncompletion of RT	Adj OR for delayed RT among DCIS patients with comorbidity: 1.88 (95% CI: 1.05–3.35) compared with patients without comorbidity. Odds for delayed RT among stage I BC patients with comorbidity: 1.14 (95% CI: 0.89–1.48) compared with patients without comorbidity. Odds for not completing RT among stage I BC patients with comorbidity: 1.28 (95% CI: 0.82–1.99) compared with patients without comorbidity	Patients with comorbidity are more likely to receive RT after a delay and to receive less than a complete course of RT.
Treatment received	CCI 0: 10% BSC, 37% BSC+RT, 53% mastectomy CCI 1: 17% BSC, 31% BSC+RT, 52% mastectomy CCI≥2: 18% BSC, 25% BSC+RT, 56% mastectomy	Patients with comorbidity are more likely to receive only BCS without RT.
Use of chemotherapy	Adj ORs compared to those with CCI = 0: CCI 1: Adj OR 0.76 (95% CI: 0.68–0.84) CCI≥2: Adj OR 0.49 (95% CI: 0.41–5.57)	Patients with comorbidity are less likely to receive chemotherapy.
Treatment received	Odds of primary appropriate therapy BMI<25: OR=1.0 (reference) BMI 25 to <30: Adj OR=1.23 (95% CI: 0.82–1.85) BMI 30 to <35: Adj OR=1.18 (95% CI: 0.73–1.91) BMI≥35: Adj OR=0.64 (95% CI: 0.33–1.23) Odds of appropriate adjuvant therapy BMI<25: OR=1.0 (reference) BMI 25 to <30: Adj OR=1.15 (95% CI: 0.81–1.64) BMI 30 to <35: Adj OR=1.09 (95% CI: 0.72–1.64) BMI≥35: Adj OR=0.96 (95% CI: 0.54–1.71)	Receipt of appropriate primary treatment and adjuvant therapy is not associated with BMI.

(*Continued*)

Table 1 (*Continued*)

Author	Design, country	Study duration	No of patients	Study population	Comorbidity assessed	% with comorbidity
McCarthy et al[142]	Cohort study, USA	1988–1999	100,311	21–62 years, stages I–IIIA	Disability	2.7%
Houterman et al[32]	Cohort study, The Netherlands	1995–1999	527	≥40 years, all stages	List of individual diseases categorized as low impact, moderate impact, high impact	N/A
Lung cancer						
Wang et al[143]	Population-based cohort study, USA	2003–2008	20,511	NSCLC, veterans ≥65 years, all stages	CCI	Overall: 81.2% CCI 1–3: 62.7% CCI≥4: 18.4%
Lüchtenborg et al[11]	Nationwide cohort study, Denmark	2005–2010	20,461	NSCLC, all stages	CCI	Overall: 49.7% CCI 1–2: 36.3% CCI≥3: 13.4%
Rueth et al[90]	Cohort study, USA	2000–2005	4,171	NSCLC, 66–80 years undergoing lobectomy, stage I	CCI	Overall: 26.4% CCI 1: 13.9% CCI≥2: 12.5%
Booth et al[101]	Cohort study, Canada	2004–2006	3,354	NSCLC, all stages	CCI	Overall: 26.7% CCI 1–2: 22.8% CCI≥3: 4.9%

End points assessed	Results related to comorbidity	Main conclusion
	Odds of appropriate hormonal therapy BMI<25: OR=1.0 (reference) BMI 25 to <30: Adj OR=1.13 (95% CI: 0.76–1.67) BMI 30 to <35: Adj OR=1.09 (95% CI: 0.69–1.73) BMI≥35: Adj OR=1.12 (95% CI: 0.58–2.16)	
Treatment received	Disabled were less likely than other women to receive BCS (Adj RR 0.80, 95% CI: 0.76–0.84), RT (Adj RR 0.83, 95% CI: 0.77–0.90), and axillary lymph node dissection (Adj RR 0.81, 95% CI: 0.74–0.90)	Disabled patients are less likely to receive BCS, RT, and axillary lymph node dissection.
Treatment received Number of complications	<70 years: treatment was not influenced by severity of comorbidity ≥70 years: patients with high comorbidity slightly more often received surgery + systemic therapy, and less surgery alone or surgery + RT (no estimates provided). 35% without comorbidity received BCS + axillary dissection vs 23% among women with high severity of comorbidity. No patients without comorbidity had two or more complications vs 6% among patients with low severity comorbidity, 10% among those with moderate severity comorbidity, and 1% among those with high severity	The association between comorbidity and treatment varies with age. Elderly patients with comorbidity receive less extensive treatment and more often have complications.
Guideline-recommended treatment	Adj rates of guideline recommended treatment Local disease: CCI 0: 60% CCI 1–3: 48.9% CCI≥4: 45.7% Regional disease: CCI 0: 38.7% CCI 1–3: 33.7% CCI≥4: 27.8% Metastatic disease: CCI 0: 27.6% CCI 1–3: 26.9% CCI≥4: 22.4%	Patients with comorbidity are less likely to receive guideline-recommended treatment.
Odds of surgical resection 1-year mortality among patients who underwent resection	Adj ORs of surgical resection compared to those with CCI=0: CCI 1–2: 0.87 (95% CI: 0.80–0.95) CCI≥3: 0.75 (95% CI: 0.67–0.85) Adj HRs of 1-year mortality compared to those with CCI=0: CCI 1: 1.14 (95% CI: 0.88–1.48) CCI 2: 1.12 (95% CI: 0.81–1.61) CCI≥3: 1.57 (95% CI: 1.17–2.12)	Patients with comorbidity are less likely to undergo surgical resection.
Postoperative complications	Adj ORs of complications compared to those with CCI 0: Any complications: CCI 1: 1.38 (95% CI: 1.15–1.66) CCI≥2: 1.83 (95% CI: 1.50–2.23) Pulmonary complications: CCI 1: 1.32 (95% CI: 1.10–1.59) CCI≥2: 1.51 (95% CI: 1.25–1.83) Cardiac complications: CCI 1: 1.36 (95% CI: 1.11–1.66) CCI≥2: 1.57 (95% CI: 1.28–1.93) Non-cardiopulmonary complications: CCI 1: 1.19 (95% CI: 0.95–1.52) CCI≥2: 1.29 (95% CI: 1.02–1.65)	The odds of any complication are increased among patients with comorbidity who undergo surgery.
Dose modification of adjuvant chemotherapy	Adj ORs compared to those with CCI 0: CCI 1–2: 1.48 (95% CI: 0.94–2.34) CCI≥3: 1.27 (95% CI: 0.35–4.58)	Patients with comorbidity are more likely to have their chemotherapy dose modified.

(*Continued*)

Table 1 (*Continued*)

Author	Design, country	Study duration	No of patients	Study population	Comorbidity assessed	% with comorbidity
Rich et al[144]	Population-based cohort study, UK	2004–2008	34,513	NSCLC, all stages	CCI	Overall: 54.9% CCI 1: 20.1% CCI 2–3: 16.9% CCI≥4: 17.9%
Cykert et al[88]	Cohort study, USA	2005–2008	386	NSCLC, early stage	List of individual diseases	N/A
Davidoff et al[107]	Cohort study, USA	1997–2002	21,285	NSCLC, ≥66 years, advanced stage	CCI	Overall: 49.6% CCI 1: 27.5% CCI 2: 12.3% CCI≥3: 9.9%
Grønberg et al[10]	Cohort study, Norway	2005–2006	436	NSCLC, stage IIIB+IV	CIRS-G[142]	Severe comorbidity: 49% Extremely severe comorbidity: 9% High severity index: 15%
Dy et al[99]	Cohort study, USA	1999–2001	4,447	Lung cancer	COPD CHF	29% COPD 13% CHF

Abbreviations: ASA, American Society of Anesthesiologists; adj, adjusted; BC, breast cancer; BCS, breast-conserving surgery; BMI, body mass index; CC, colon cancer; CCI, Charlson Comorbidity Index; CHF, chronic heart failure; CIRS-G, Cumulative Illness Rating Scale for Geriatrice; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; DCIS, ductal carcinoma in situ; DVT, deep venous thrombosis; HR, hazard ratio; N/A, not available; NSCLC, non-small-cell lung cancer; OR, odds ratio; RR, relative risk; RT, radiation therapy.

For patients with breast cancer, the 5-year HR for CCI score ≥3 vs CCI score of 0 was 0.48 (95% CI: 0.21–1.07), and for patients with colorectal cancer, the 5-year HR for CCI score ≥3 vs CCI score of 0 was 1.00 (95% CI: 0.76–1.33). In contrast, Land et al[6] recently found an association between comorbidity and cancer-specific mortality in women with breast cancer (HR for CCI score ≥3 vs CCI score of 0 = 1.79 [95% CI: 1.66–1.93]). Median follow-up time in the study was 8.2 years. Berglund et al[38] found a similar association in women with early-stage breast cancer

End points assessed	Results related to comorbidity	Main conclusion
Odds of having surgery	Adj ORs compared to those with CCI 0: CCI 1: 0.95 (95% CI: 0.86–1.04) CCI 2–3: 0.89 (95% CI: 0.80–0.99) CCI≥4: 0.67 (95% CI: 0.56–0.80)	Patients with comorbidity are less likely to undergo surgical resection.
Surgery within 4 months of diagnosis	Adj OR of surgery compared to those with <2 comorbidities: ≥2 comorbidities: 0.42 (95% CI: 0.22–0.84)	Patients with comorbidity are less likely to undergo surgery within 4 months of diagnosis.
Receipt of (1) any chemotherapy within 90 days and (2) single agent, relative to platinum-based doublet therapy	Adj ORs of chemotherapy compared to those with CCI 0: CCI 1: 1.05 (95% CI: 0.97–1.13) CCI 2: 0.91 (95% CI: 0.80–1.02) CCI≥3: 0.74 (95% CI: 0.64–0.86)	Patients with comorbidity are less likely to receive chemotherapy, including platinum-based doublet therapy.
2-year survival benefit associated with treatment	Adj ORs of single agent compared with platinum-based doublet therapy: CCI 1: 1.16 (95% CI: 0.99–1.36) CCI 2: 1.45 (95% CI: 1.15–1.83) CCI≥3: 1.43 (95% CI: 1.05–1.96) Adj HRs of 2-year mortality comparing treated vs untreated patients: CCI 0: 1.0 (reference) CCI 1: 1.06 (95% CI: 1.03–1.09) CCI 2: 1.12 (95% CI: 1.08–1.55) CCI≥3: 1.17 (95% CI: 1.12–1.22)	
Receipt of chemotherapy Receipt of toxicity	Patients with severe comorbidity vs patients without severe comorbidity: Mean number of chemotherapy cycles: 3.2 vs 3.5 Completed all four cycles: 65% vs 73% Completed cycles without delay: 46% vs 59% Dose reductions: 29% vs 35% Second line systemic therapy: 27% vs 26% RT: 35% vs 48% Toxicity: Grade 3–4 thrombocytopenia: 46% vs 36% Thrombocytopenic bleedings: 3% vs 4% Grade 3–4 neutropenia: 48% vs 42% Neutropenic fevers: 12% vs 5% Death from neutropenic infection: 3% vs 0%	Patients with comorbidity are less likely to complete all cycles of chemotherapy and have slightly more dose reductions. Thrombocytopenia and neutropenia are slightly more frequent among patients with comorbidity.
Receipt of surgery, chemotherapy, and RT	Adj ORs compared to patients with neither COPD nor CHF: OR of surgery to resect lung cancer COPD: 0.66 (95% CI: 0.52–0.83) COPD: 0.28 (95% CI: 0.15–0.50) OR of receiving adjuvant chemotherapy COPD: 0.74 (95% CI: 0.62–0.89) COPD: 0.66 (95% CI: 0.46–0.96) OR of RT COPD: 1.02 (95% CI: 0.86–0.89) COPD: 0.91 (95% CI: 0.66–1.27)	Patients with COPD or CHF are less likely to undergo surgery and more likely to receive chemotherapy but not RT.

(stage I: HR for CCI score ≥2 vs CCI score of 0 = 1.47 [95% CI: 1.11–1.94]), but not in women with more advanced cancer (stage IIB: HR for CCI score ≥2 vs CCI score of 0 = 0.83 [95% CI: 0.63–1.10]). Several other studies have found an association between increasing levels of comorbidity and higher cancer-related mortality among patients with colon, breast, or lung cancer.[8,9,25,39–41] However, there is considerable uncertainty in defining whether death was due to the cancer or to other causes (including comorbidity), and the validity of cause-of-death data may be questioned.[42–44]

Effect of comorbidity on survival

Comorbidity can affect cancer survival through its impact on such factors as cancer detection, treatment, and adherence.[45] In the following sections, we focus on the potential role of comorbidity on different points from cancer detection through diagnosis and treatment.

Impact of comorbidity on cancer morphology, histology, differentiation, and proliferation status

It is plausible that comorbidity is associated with differences in morphology, histology, differentiation, and proliferation status. Cancer risk is elevated in patients with obesity; in patients with diabetes and resulting insulin resistance and chronic hyperinsulinemia;[46–49] and in patients with inherited, acquired (eg, from HIV/AIDS), or drug-induced (eg, from treatment with steroids or biologics) immunosuppression.[50,51] Some of these risk factors also may be associated with rate of cancer growth and cancer grade/differentiation and thus with prognosis. Conversely, drugs such as nonsteroidal anti-inflammatory agents,[52,53] aspirin,[54,55] statins,[56] and long-term antibiotics used to treat comorbidity-associated infections[57] may decrease cancer incidence,[52–55] progression,[53,56] and risk of recurrence and improve cancer prognosis.[58–61]

As shown in Table 2, the proportion of squamous cell carcinoma in lung cancer patients with comorbidity has been found to be 6%–11% higher than in patients without comorbidity.[10,11] Chlebowski et al[62] found a slightly higher proportion of ductal breast cancer (69% vs 65%) and a slightly lower proportion of estrogen-receptor-positive breast cancer (74% vs 78%) and progesterone-receptor-positive breast cancer (61% vs 64%) among diabetic compared with nondiabetic breast cancer patients (Table 2). Kaplan et al[63] also found a higher incidence of ductal breast cancer among diabetics compared with nondiabetics (89% vs 82%). In contrast, Land et al[6] found no differences in histology or receptor status according to level of comorbidity. However, few studies provided data on tumor biology by comorbidity level.

Comorbidity and other patient characteristics

Age is closely related to comorbidity and is also a strong predictor of mortality in cancer patients. Thus, older age could potentially explain the prognostic impact of comorbidity. However, the association between comorbidity and cancer survival persists even after adjusting for age. The association also remains after adjusting for other prognostic factors, such as cancer stage and treatment.[64] It is also plausible that age may modify the relationship between comorbidity and cancer survival if clinicians tend to focus more on comorbidity in older than in younger patients when deciding on type of cancer treatment.[65] Sex may also play a role, as several studies have indicated that women with lung cancer have a better prognosis than men with lung cancer.[66–68] The underlying reasons are debated and remain unresolved. In addition, converging evidence from epidemiological studies conducted in a variety of settings have documented racial and socioeconomic disparities in cancer survival.[67–74] Multiple factors may contribute to these disparities, but comorbidity seems to play an important role.[72–77] In a US cohort study of 906 women with breast cancer, Tammemagi et al[78] found an HR for all-cause mortality of 1.14 (95% CI: 0.92–1.40) for blacks compared to whites after adjusting for age, tumor stage, estrogen receptor status, surgery, chemotherapy, and radiation therapy. After further adjustment for comorbidity, the HR decreased to 1.02 (95% CI: 0.83–1.27). The two most important comorbidities explaining the disparities were diabetes and hypertension.[78] A Danish cohort study conducted by Dalton et al[79] found an interaction between income and comorbidity, resulting in 15% lower survival within 10 years after primary surgery for early-stage breast cancer among women of low socioeconomic status with comorbid conditions (~65%) compared to more affluent women with similar comorbid conditions (~80%). This suggests a differential effect of comorbidity on risk of dying of early-stage breast cancer by socioeconomic group.[75]

Impact of comorbidity on stage at diagnosis

It is often argued that comorbidities may be associated with late-stage cancer diagnosis because they may mask early cancer symptoms. Dementia,[80,81] alcohol consumption,[82,83] and major depression[84] have been associated with late-stage diagnosis of colon cancer and breast cancer. However, as shown in Table 3, several studies have found a higher prevalence of comorbidity in patients diagnosed with early-stage lung cancer, breast cancer, and colorectal cancer. Earlier cancer diagnosis in patients with comorbidities is plausible because these patients are more likely to require frequent medical care, and hence to receive closer clinical monitoring, than persons without comorbidities. Nonetheless, the association between comorbidity and earlier diagnosis seems to depend on the specific comorbid condition. Fleming et al[85] found that women with cardiovascular disease, musculoskeletal disease, gastrointestinal disease, osteoarthritis, and genitourinary disease had a 7%–24% lower risk of being diagnosed with advanced breast cancer (Table 3). In contrast, women with diabetes, renal disease, other endocrine

Table 2 Results of selected studies on the association between comorbidity and cancer characteristics

Author, country	Study duration	No of patients	Cancer site	Cancer characteristics, %				Main conclusion
Lüchtenborg et al,[11] Denmark	2005–2010	20,461	NSCLC	**Histology**	**CCI score[22] 0**	**CCI scores 1–2**	**CCI score ≥3**	No difference in histological type by CCI score.
				Adenocarcinoma	29	26	26	
				Non-small-cell	13	12	14	
				Small cell	12	12	10	
				Large cell	3	3	2	
				Squamous cell	17	21	23	
				Carcinoid	1	0	0	
				Other specified	1	1	1	
				Unspecified	12	11	11	
				Unknown	12	14	13	
Chlebowski et al,[62,b] USA	NA	3,273	BC			**No diabetes**	**Diabetes**	No difference in histological type or receptor status between diabetics and nondiabetics.
				Histology				
				Ductal		65	69	
				Lobular		9	9	
				Ductal and lobular		13	8	
				Tubular		3	0.1	
				Other		10	12	
				ER status				
				Positive		78	74	
				Negative		14	16	
				Borderline		0.1	0.1	
				Unknown		8	9	
				PR status				
				Positive		64	61	
				Negative		26	27	
				Borderline		0.6	0.2	
				Unknown		9	10	
				HER2				
				Positive		12	14	
				Negative		59	61	
				Borderline		0.7	<0.1	
				Unknown		29	25	
				Triple-negative status[a]				
				Triple-negative		6	9	
				Other		64	66	
				Unknown		30	26	

(*Continued*)

Table 2 (*Continued*)

Author, country	Study duration	No of patients	Cancer site	Cancer characteristics,%					Main conclusion
Land et al,[6] Denmark	1990–2008	62,591	BC	**ER status**	**CCI 0**	**CCI 1**	**CCI 2**	**CCI ≥3**	No difference in ER receptor status or histological type by CCI score.
				Negative	21	18	19	21	
				Positive	72	76	74	74	
				Unknown	7	6	7	5	
				Histology + gr					
				Ductal, gr I	25	26	24	24	
				Ductal, gr II	35	31	33	33	
				Ductal, gr III	19	17	19	19	
				Ductal, gr unknown	2	2	2	2	
				Lobular	11	12	12	12	
				Others	7	8	8	8	
				Unknown	1	1	2	2	
				Fascial invasion					
				No	93	94	93	94	
				Yes	4	4	4	3	
				Unknown	3	2	3	3	
Huang et al,[146] Taiwan	2002–2008	1,197	CRC	**Differentiation**		**No diabetes**		**Diabetes**	No difference in tumor differentiation between diabetics and nondiabetics.
				Well		8		7	
				Moderate		81		82	
				Poor		13		11	
Kaplan et al,[63] Turkey	1998–2010	483	BC	**Histology**		**No diabetes**		**Diabetes**	No difference in histological type or receptor status between diabetics and nondiabetics.
				Ductal		82		89	
				Lobular		10		4	
				Other		8		7	
				ER status					
				Positive		56		54	
				Negative		44		46	
				PR status					
				Positive		59		59	
				Negative		41		41	
				HER2 overexpression					
				Positive		48		59	
				Negative		52		41	
				Tumor size					
				<5 cm		83		82	
				≥5 cm		17		19	

Grønberg et al,[10] Norway	2000–2006	436	NSCLC	**Histology**	**No severe comorbidity**	**Severe comorbidity**	Patients with severe comorbidity more often had squamous cell carcinoma.
				Squamous cell carcinoma	19	30	
				Adenocarcinoma	52	48	
				Large cell carcinoma	5	7	
				Other	23	15	

Notes: [a]Triple negative = ER-negative, PR-negative, HER2-negative. [b]Based on the Women's Health Initiative clinical trials which includes four clinical trials and an observational study.
Abbreviations: BC, breast cancer; CC, colon cancer; CCI, Charlson Comorbidity Index; CRC, colorectal cancer; ER, estrogen receptor; gr, grade; HER2, human epidermal growth factor; NSCLC, non-small-cell lung cancer; PR, progesterone receptor; NA, not applicable.

disorders, psychiatric disease, osteoporosis, hematologic disease, obesity, and AIDS had an 11%–20% higher risk of being diagnosed with advanced disease (Table 3).[85] Similarly, Yasmeen et al[76] found that presence of certain comorbidities (eg, arthritis, depression, diabetes, stable coronary artery disease) was associated with higher utilization of screening mammograms and greater likelihood of diagnosis of localized disease (odds ratio [OR] = 0.8, 95% CI: 0.7–0.9), while a group of other comorbidities judged to be more serious (including severe heart failure, cardiac arrhythmias, and end-stage pulmonary disease) was associated with less screening mammography and later stage at diagnosis (OR = 1.3, 95% CI: 1.2–1.4) (Table 3).[76] Studies relating comorbidity to breast cancer screening have had mixed results, showing either increased or decreased risk of late-stage disease according to comorbidity burden.[76,86]

Impact of comorbidity on choice of treatment

As shown in Table 1, surgical management steadily declines with increasing comorbidity regardless of cancer site and disease stage. Berglund et al[38] found that the OR of no surgery was 1.88 (95% CI: 1.65–2.14) among breast cancer patients with a CCI score of 1, and 3.01 (95% CI: 2.67–3.41) among those with a CCI score ≥2, compared with patients without comorbidity. In a population-based cohort study conducted in Northern Denmark, Iversen et al[5] found that 83.8% of colon cancer patients with a CCI score of 0 undergo surgical resection, compared with 77.7% of patients with CCI scores of 1 or 2 and 63.2% of patients with a CCI score ≥3. Similarly, other studies have reported 25%–58% lower odds of surgical resection in lung cancer patients with severe comorbidity compared with patients without comorbidity.[11,87,88] An increased risk of complications among patients with comorbidities who undergo surgical resection for colon cancer (adjusted OR for body mass index of 30–49 = 1.26 [95% CI: 1.05–1.49]; for chronic obstructive pulmonary disease [COPD] = 1.84 [95% CI: 1.49–2.27]; and for high ASA physical classification score = 1.65 [95% CI: 1.26–2.16]),[89] for breast cancer (6% with low comorbidity had complications vs 10% with moderate comorbidity),[32] and for lung cancer (adjusted OR for a CCI score of 1 = 1.38 [95% CI: 1.15–1.66] and for a CCI score ≥2 = 1.83 [95% CI: 1.50–2.23]),[90] compared with patients without comorbidity (Table 3). Other studies have reported 2- to 4-fold higher 30-day postoperative mortality rates in colon cancer patients with comorbidity compared to patients without comorbidities.[89,91]

Patients with comorbidities are less likely to receive any adjuvant chemotherapy,[92–99] more likely to receive a reduced

Table 3 Results of selected studies on the association between comorbidity and cancer stage at diagnosis

Author, country	Study duration	No of patients	Cancer site	Stage at diagnosis, %					Main conclusion
Lüchtenborg et al,[11] Denmark	2005–2010	20,461	NSCLC		**I**	**II**	**III**	**IV**	Patients with comorbidities have less advanced NSCLC.
				CCI 0	15	6	28	47	
				CCI 1–2	18	6	28	45	
				CCI ≥3	20	6	27	43	
Wang et al,[143] USA	2003–2008	20,511	NSCLC		**Local**	**Regional**		**Metastatic**	Patients with comorbidities have less advanced NSCLC.
				CCI 0	16	19		21	
				CCI 1–3	64	64		61	
				CCI ≥4	20	17		18	
Nagel et al,[147] Germany	2004–2007	566	CC		**I**	**II**	**III**	**IV**	Patients with T2DM have less advanced CC.
				No T2DM	24	35	26	16	
				T2DM	25	46	20	9	
Dalton et al,[70] Denmark	2001–2008	18,103	SCLC + NSCLC		**Adj OR of advanced disease (95% CI)**				Patients with comorbidities have lower odds of advanced lung cancer.
				CCI 0	1.0 (ref)				
				CCI 1	0.88 (0.83–0.92)				
				CCI 2	0.84 (0.77–0.92)				
				CCI ≥3	0.73 (0.65–0.81)				
Yasmeen et al,[76] USA	1993–2005	118,742	BC		**Local**	**Advanced**		**Unknown**	Patients with stable comorbidity have less advanced disease while those with unstable comorbidity have slightly more advanced disease.
				Stable comorbidity					
				CCI 0	70	19		11	
				CCI 1	80	11		9	
				CCI 2	81	10		9	
				CCI ≥3	81	10		9	
				Unstable comorbidity					
				CCI 0	79	12		9	
				CCI 1	78	12		11	
Morris et al,[91] UK	1998–2006	162,920	CRC		**Duke A**	**Duke B**	**Duke C**	**Duke D**	Patients with comorbidities have less advanced CRC.
				CCI 0	11	33	32	9	
				CCI 1	8	35	34	9	
				CCI 2	11	36	32	8	
				CCI 3	9	37	32	6	
Pagano et al,[148] Italy	2000–2003	2,298	NSCLC			**Early**		**Advanced**	Patients with comorbidities have less advanced NSCLC.
				CCI 0		54		64	
				CCI >0		47		36	
Grønberg et al,[10] Norway	2000–2006	436	NSCLC			**IIIB**	**IV**		Patients with comorbidities have less advanced NSCLC.
				–Severe comorbidity		23	77		
				+Severe comorbidity		35	65		
Cronin-Fenton et al,[4] Denmark	1995–2005	9,300	BC		**Local**	**Regional**	**Metastatic**	**Unknown**	Patients with comorbidities have more unstaged BC.
				CCI 0	47	28	6	5	
				CCI 1–2	43	35	8	16	
				CCI ≥3	47	32	7	15	

McCarthy et al,[142] USA	1995–2001	8,966	BC		**I**	**IIA**	**IIB**	**IIIA**	No difference in stage according to disability.
				–Disability	48	30	17	5	
				+Disability	50	29	16	5	
Fleming et al,[85] USA	1993–1995	17,468	BC			**Adj OR of advanced disease**			The odds of advanced disease are dependent on the specific comorbid condition.
				Cardiovascular disease		0.83			
				Benign hypertension		0.93			
				Malignant hypertension		1.01			
				Cerebrovascular disease		1.04			
				Renal disease		1.12			
				Diabetes		1.17			
				Endocrine disease		1.10			
				Neurological		1.00			
				Psychiatric		1.27			
				Osteoarthritis		0.93			
				Osteoporosis		1.14			
				Musculoskeletal		0.85			
				Pulmonary, mild/moderate		1.01			
				Pulmonary, severe		0.99			
				GI, mild/moderate		0.79			
				GI, severe		0.94			
				Hematologic		1.23			
				Genital–urinary		0.82			
				Obesity		1.17			
				AIDS		1.25			
				Rheumatologic		0.96			
				Other cancers		0.94			

Abbreviations: adj, adjusted; BC, breast cancer; CC, colon cancer; CCI, Charlson Comorbidity Index; CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; NSCLC, non-small-cell lung cancer; OR, odds ratio; SCLC, small-cell lung cancer; T2DM, type 2 diabetes mellitus.

dose,[10,100,101] and more likely not to complete chemotherapy treatment when initiated[101,102–104] (Table 1). While some studies report that patients with comorbidity are less likely to be referred to a medical oncologist,[95,105] a US cohort study of 4,765 colon cancer patients found that patients with comorbidity who underwent resection consulted an oncologist more frequently than patients without comorbidity (adjusted OR for consultation among patients with a CCI score of 1 = 1.25 [95% CI: 0.98–1.59] and among patients with a CCI score ≥2 = 1.61 [95% CI: 1.17 to 2.20]).[94] However, in another US study, colon cancer patients with comorbidity were less likely to receive chemotherapy, whether or not they consulted an oncologist (Table 1).[95] Presence of comorbidity has also been associated with increased time from cancer detection to surgical resection or initiation of chemotherapy or radiotherapy.[88,95,104,106,107] The reasons for this remain unknown.

There are few data on the impact of comorbidity on risk of complications after chemotherapy and radiation therapy. Grønberg et al[10] found that lung cancer patients with severe comorbidity were more likely than lung cancer patients without comorbidity to develop thrombocytopenia (46% vs 36%) or febrile neutropenia (12% vs 5%) or to die of neutropenic infection (3% vs 0.%) following chemotherapy treatment. Conversely, Gross et al[108] found that risk of hospitalization attributable to chemotherapy treatment was lower among colon cancer patients with COPD, chronic heart failure, or diabetes, compared with patients without these conditions (Table 1).

Impact of comorbidity on health care-related factors

Treatment in specialized medical centers or by a high-volume surgeon has been associated with improved treatment and survival.[109–114] However, there are very few studies on the prognostic impact of receiving high-volume-cancer-center care and highly specialized treatment in relation to comorbidity. A US study of 211,084 patients with lung, breast, colorectal, and prostate cancer found that patients treated at National Cancer Institute-designated cancer centers had lower mortality than patients treated at volume-matched hospitals across all levels of comorbidity (3-year mortality for specialized vs nonspecialized treatment: adjusted OR for CCI score of 0 = 0.89 [95% CI: 0.85–0.98]; adjusted OR for CCI score of 1 or 2 = 0.87 [95% CI: 0.80–0.95]; adjusted OR for CCI score ≥3 = 0.83 [95% CI: 0.74–1.00]).[111] Furthermore, while some studies have shown a social gradient in access to specialized cancer care,[114,115] few studies have examined potential disparities in access to specialized care among patients with comorbidities.

To better understand the observed underutilization of treatment by age and comorbidity, a number of studies have explored physician and patient perspectives regarding the decision to use adjuvant chemotherapy.[105,116–119] It has been found that 24%–70% of cancer patients with comorbidity are not treated according to guidelines.[105,118,120–122] In a US national survey of surgeons and medical oncologists caring for patients with colorectal cancer, physicians agreed with guidelines recommending adjuvant chemotherapy for young, otherwise healthy patients with stage III colon cancer, but differed widely on recommendations for patients with comorbid illnesses.[119] Comorbidity is the most frequent reason for nonreceipt of cancer treatment cited in the medical charts of patients with lung (68% of nontreated patients) and colorectal (47% of nontreated patients) cancer.[117,118] To some extent, this finding probably reflects concern about toxicity in patients with comorbidity. Among patients with lung cancer, Gironés et al[123] recently showed that withholding treatment was associated with factors such as poor health, advanced age, depression, and dementia, but not related to symptoms at diagnosis or cancer stage.

Physicians' motivations and treatment barriers are also influenced by age, race, and education level. Studies have shown that duration of consultations and amount of information provided to patients increases with higher education levels.[124–126] While patient perceptions and preferences play a role in treatment decisions and outcomes, the treating physician's recommendation has been found to be a major determinant of patients' preferences for chemotherapy.[127,128] It remains unclear whether patient preferences differ according to level of comorbidity.

Influence of comorbidity on treatment regimen completion

Patients with comorbidities may be compromised in their ability to comply with treatment regimens or to tolerate their side effects. In a US cohort study of 3,733 colon cancer patients aged ≥65 years with records in the linked SEER-Medicare dataset during 1995–1999, comorbidity was associated with lower odds of completing adjuvant chemotherapy (adjusted ORs were 0.75 [95% CI: 0.60–0.97] for patients with one comorbidity and 0.62 [95% CI: 0.46–0.84] for patients with >1 comorbidity) compared with patients without comorbidity.[129] Several other studies have also shown that comorbidity is associated with decreased likelihood of completing chemotherapy treatment among patients with colon,[1,102,108] breast,[100] and lung cancer[10] (Table 1). However, none of these studies examined whether failure to complete

chemotherapy was related to poorer adherence or to level of side effects. Many studies of women with early-stage breast cancer, based on pharmacy, medical, and health insurance data, have reported high rates of discontinuation of adjuvant tamoxifen, ranging from 35%–51% during study periods of 3.5–5 years.[130–133] Patient refusal reportedly accounts for a third of occurrences of treatment underuse,[134] and comorbidity has been identified as a predictor of discontinuation and nonadherence to regimens of tamoxifen and aromatase inhibitors.[132,133] However, a very recent German cohort study of 12,412 women with breast cancer, among whom 7,312 were treated with tamoxifen, demonstrated lower rates of tamoxifen discontinuation among patients with diabetes (adjusted HR = 0.81 [95% CI: 0.75–0.86]) and depression (adjusted HR = 0.92 [95% CI: 0.87–0.97]).[135]

Methodological considerations

Several methodological concerns must be considered when evaluating the summary evidence from the studies reviewed above. This review is not a systematic review. A research librarian assisted our searches, but we did not use explicit predefined criteria to select the articles included. Thus, our study selection was subjective and we may have missed relevant papers. The studies included were heterogeneous and included vastly different patient populations (Tables 1–3). Moreover, many were designed as predictive studies and included a wide range of potential prognostic factors besides comorbidity in regression models. Some studies also included variables such as patient performance status (activities of daily living),[136] which may constitute an intermediate variable in the causal path from comorbidity to cancer survival. Adjusting for patient performance status thus may weaken the prognostic impact of comorbidity. A further challenge in summarizing the effect of comorbidity on cancer survival was inconsistent definitions of comorbidity. Comorbidity was measured in different ways in the studies under review, referring either to one specific disease or aggregation of several diseases using an index. Moreover, indices varied from general comorbidity measures to disease-specific measures. Most studies aggregated comorbidity into a comorbidity index (most frequently the CCI) (Table 1) with little consideration of how specific conditions affected outcomes. Although shown repeatedly to be a valid prognostic predictor, the CCI itself is based on simple assumptions about mortality risk when various conditions co-occur. In addition, most studies collapsed the CCI score of above a certain threshold into a single open-ended category (eg, 0, 1–2, and ≥3) to improve comprehension and the statistical efficacy of the analysis

Is the negative prognostic impact of comorbidity attributable to comorbidity-related deaths or does comorbidity also influence cancer-specific mortality?
How is tumor biology influenced by comorbidity?
How much of the negative prognostic impact of comorbidity is explained by differences in socioeconomic position, lifestyle, and social support?
Is comorbidity associated with less access to specialized care?
Does treatment at increasingly specialized cancer centers improve cancer survival mainly in patients without severe comorbidity?
Are apparent disparities in cancer treatment among patients with comorbidity related to physician recommendations, patients' preferences, and/or decreased compliance?
Is comorbidity associated with higher risk of cancer treatment toxicity, given the limited participation of patients with comorbidity in randomized clinical trials?
How do individual comorbidities – alone and in combination – impact cancer patients' clinical courses?
Does the prognostic effect of specific comorbidities vary according to cancer type?
How do duration and severity of comorbidity influence cancer prognosis?
How is comorbidity most accurately measured in cancer patients?

Figure 2 Some unanswered questions regarding the prognostic impact of comorbidity in cancer patients.

(the prevalence of patients with high CCI scores is low in most study populations). The effect of the combined category is a weighted average of the individual scores.[23] Analyses based on individual comorbid diseases would avoid these assumptions but are difficult to conduct, as they require much larger cohorts to identify subgroups with specific conditions of sufficient size.[137] It must also be noted that virtually none of the studies under review examined the impact of duration and/or severity of comorbidity on cancer prognosis.

Most studies in our review were based on analyses of population-based cancer registry data linked with administrative data. Such data are generally adequate for determining prevalence of comorbidity and survival outcomes, but generally provide limited information on treatment delivery or patient tolerance for treatment regimens. Furthermore, studies relying on such databases may miss important comorbidities, underestimate their severity, or fail to address confounding factors such as smoking and other lifestyle factors. Thus, to improve research on comorbidity, studies should include information from different data sources (ie, administrative data, chart review, prescription records, and records of general practitioners) to provide more information on level and severity of comorbidity.

Conclusion

Despite increasing recognition of the impact of comorbid illnesses on the prognosis of cancer patients, challenges remain. A large number of studies reported suboptimal treatment among patients with comorbidity across tumor sites and stages of disease. However, because most studies examined diagnosis, treatment, physician and/or patient preferences, but not all factors, it is unclear whether suboptimal cancer treatment reflects appropriate consideration of increased risk of toxicity due to comorbid illness, patient preferences, lower quality of clinical care, or poor adherence. Consequently, a number of questions remain unanswered about the relationship between comorbidity and cancer outcome (Figure 2). To adequately address these questions, studies are needed that elucidate whether comorbidity in general or only specific diseases or disease combinations are associated with poorer survival. Thus, studies with a more specific focus should be undertaken, including those that address the impact of an individual comorbidity on treatment provided to a homogenous population of cancer patients (ie, with comparable stage and tumor type).

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The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 PubMed search strategy

Subject	Query	Articles retrieved
The cancer		
1	"Colonic Neoplasms" [Majr]	46042
2	"Breast Neoplasms" [Majr]	162698
3	"Lung Neoplasms" [Majr]	120655
Comorbidity		
4	"Comorbidity" [MeSH]	56994
5	Comorbid*	97741
6	Multimorbid*	871
7	"Coexisting diseases"	312
8	4 OR 5 OR 6 OR 7	98580
9	"Diabetes Mellitus" [MeSH]	285993
10	"Cardiovascular Diseases" [MeSH]	1743728
11	"Pulmonary Disease, Chronic obstructive" [MeSH]	18784
12	"Dementia" [MeSH]	106404
13	9 OR 10 OR 11 OR 12	2063851
14	8 OR 13	2137251
Outcome		
15	Prognos*	508580
16	Surviv*	829260
17	Mortality	761245
18	"Mortality" [MeSH]	253258
19	15 OR 16 OR 17 OR 18	1625050
Combined colon cancer query	1 AND 14 AND 19	268
Combined breast cancer query	2 AND 14 AND 19	1222
Combined lung cancer query	3 AND 14 AND 19	1612