民間の平均給与(年額)は1999年の461.3万円から2009年の405.9万円と，10年間に12%減少している(国税庁「民間給与実態統計調査」)。患者負担は相対的にも重くなっていることがうかがえる。

がん患者の経済的負担の実態は，十分には把握されていない。診療報酬明細書(レセプト)は，全国レベルで患者負担を把握する有力な手段となりうるが，現行のシステムは月単位の診療報酬請求を目的とした，保険者別，施設別データであるため，これから年間の患者負担を捉えることは容易ならない。そこで，患者自身に，家計簿や領収書をみながら，がん医療にかかる負担額を記入してもらう多施設共同の大規模調査(2004～2011年)を実施した[1)]。

がん患者の自己負担額(窓口負担などの直接費用＋健康食品や民間保険の保険料などの間接費用)は平均101万円である。一方，償還・給付額(民間保険の給付金＋高額療養費＋医療費還付)は平均63万円で，自己負担額との差額38万円が実質的な負担額である(**図8**)。これを治療法別にみると，化学療法，放射線療法における自己負担額は，全体の約1.3倍である。

大腸癌の経済的負担

大腸癌患者の自己負担額(直接＋間接費用)の分布をみると，平均値は94.1万円，中央値は65.6万円，最頻値は45万円である。少額の患者が多いものの，広いスコープに分布していることがわかる。直接費用，間接費用の平均値は各75.5万円，23.1万円，中央値は各51.9万円，10.5万円である(**図9**)。これらは，合計欄に記載された金額を単純平均(0除く)した数値であり，項目別金額と該当者の割合を用いる以下の平均値とは計算方法が異なる。

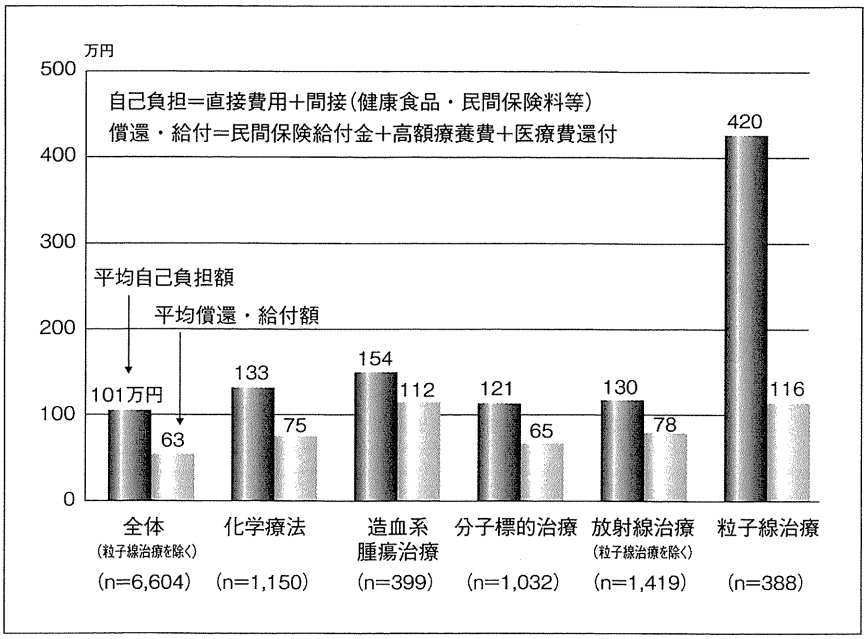

図8　治療法別にみたがん患者の自己負担額と償還・給付額(年間)

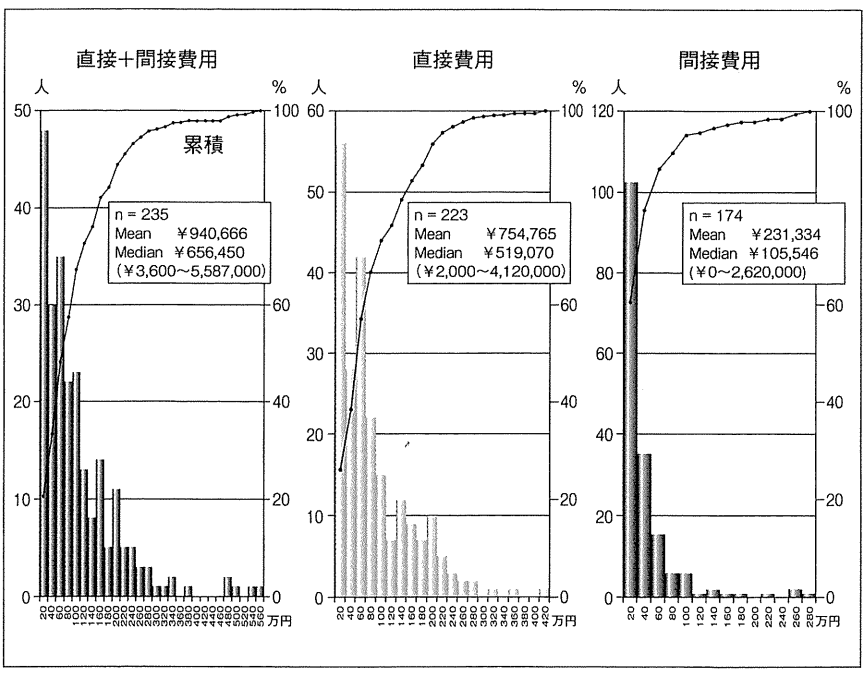

図9　大腸癌患者の自己負担額分布

(2010～11年調査)

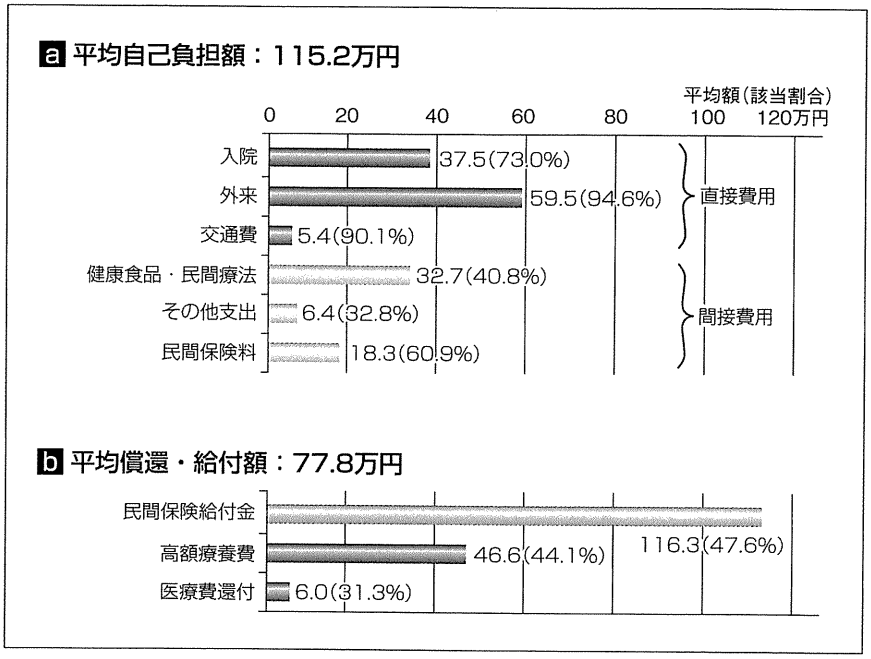

図10　大腸癌患者の自己負担額と償還・給付額(年間)
n＝250
n：回答者数，該当割合：実額回答者数/有効回答数＊100%

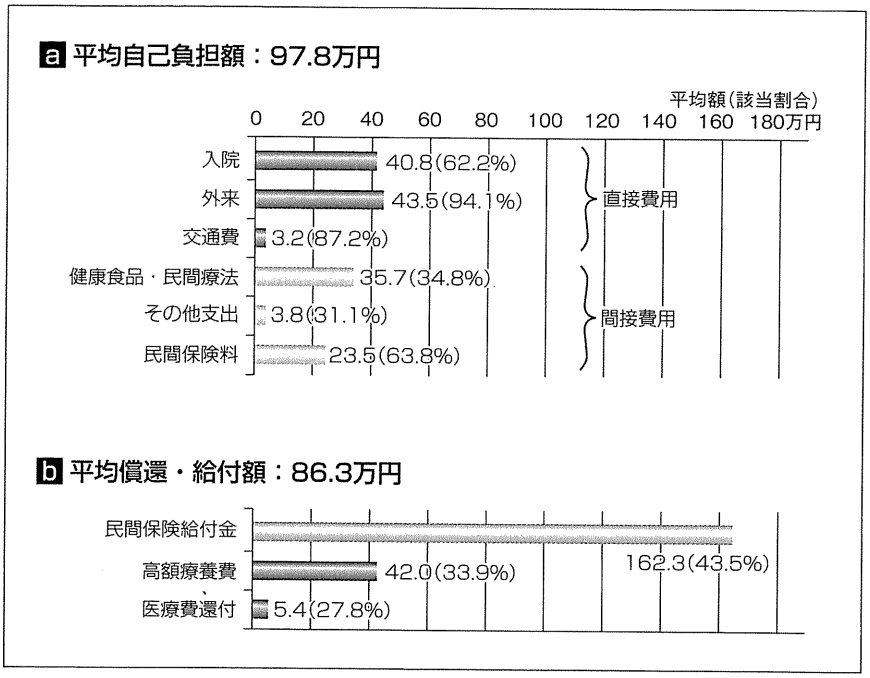

図11　stage Ⅲ大腸癌患者の自己負担額と償還・給付額(年間)
n＝59

大腸癌患者(n＝250，平均年齢64.4±10.5歳，男61.6%，初回診断時期41.8±67.7ヵ月前)の自己負担額を内訳別にみると，1年間に患者の73%が入院し，その費用の平均は37.5万円，外来費用の平均は59.5万円である(**図10**)。現在受けている，またはこれまで受けた治療(複数回答)は，手術が88.2%，分子標的薬以外の化学療法が59.3%，分子標的治療が46.3%，内視鏡治療が27.2%，放射線治療が5.3%である。

間接費用では，患者の40.8%で健康食品や民間療法の支出があり，その支出額の平均は32.7万円で，入院費用にも匹敵する水準である。各項目の平均値に該当割合を乗じ，これを足し合わせると自己負担額の平均が算出される。大腸癌では115.2万円である。

一方，大腸癌患者の償還・給付額を内訳別にみると，44.1%の患者が高額療養費を利用し，その償還額の平均は46.6万円である。約半数の患者が，がん保険など民間保険の給付金を受けており，その平均額は116.3万円である。がんの診断があった場合に診断給付金が100万円程度支給される保険商品が多く，これらの給付金を受けたものと考えられる。民間保険は公的保険を補完するものであるが，半数近くのがん患者は，この給付金によって大きな負担の軽減がはかられていることがうかがえる。

stage別にみると，平均自己負担額はstage Ⅲでは97.8万円であるのに対しstage Ⅳでは164.3万円に増加する(**図11，12**)。重症化するにつれ，入院，外来の費用ばかりでなく，健康

食品や民間療法の支出も大きくなることが読み取れる。stage Ⅳでは，外来の費用が入院の2倍であり，薬物治療が主に外来で実施されている状況がうかがえる。分子標的治療を受けるがん患者の自己負担額は，これに用いる薬剤が高額なため，大きくなることが多く，自己負担額から民間保険給付金などの償還・給付額を差し引いても，負担は少なくない。

重くなる経済的負担

高額療養費制度の利用者は，大腸癌患者の8割を占める(**図13**)。これは，治療費が高額となった場合，一定の自己負担限度額を超える部分を償還払いする(手続きをすれば入院分は現物支給)制度である。保険制度本体(1～3割の患者負担)を補完するセーフティー・ネットであるが，今や多くの患者にとってなくてはならない制度となっている。

高額療養費制度で，患者負担をどの程度軽減されているかを自己負担額の分布でみると，直接費用の平均値75.5万円，中央値51.9万円が，直接費用から高額療養費償還額を減じた負担額(この制度を利用しない者は0円として算出)では，各51.1万円，40.2万円に減少する。

高額療養費制度は1973(昭和48)年に創設されたが，その後さまざまな運用上の規定が設けられ，利用者にわかりにくい複雑な制度となっている。しかし，約6割の利用者が，入院分が現物支給となる限度額適用認定証を

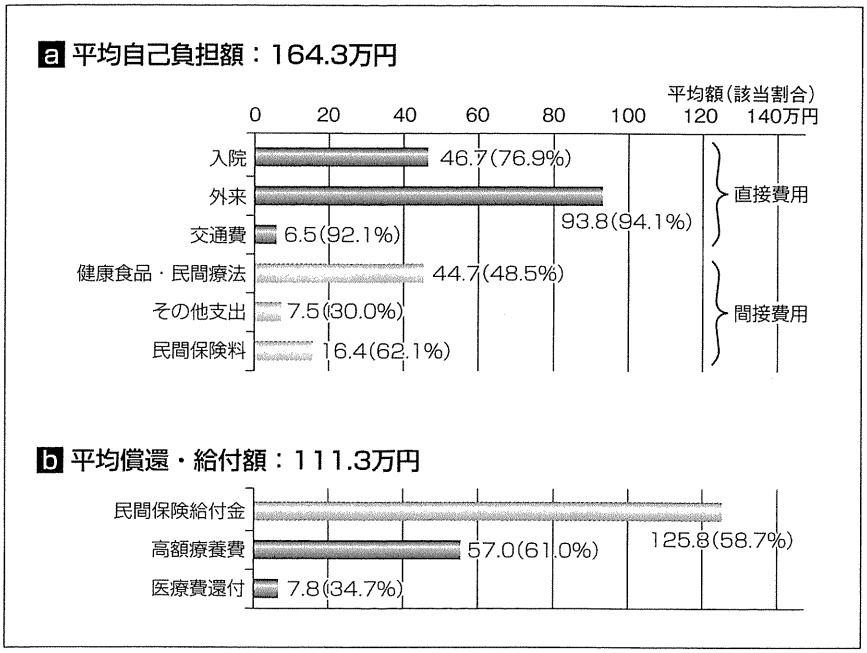

図12　stage Ⅳ大腸癌患者の自己負担額と償還・給付額(年間)
n＝77

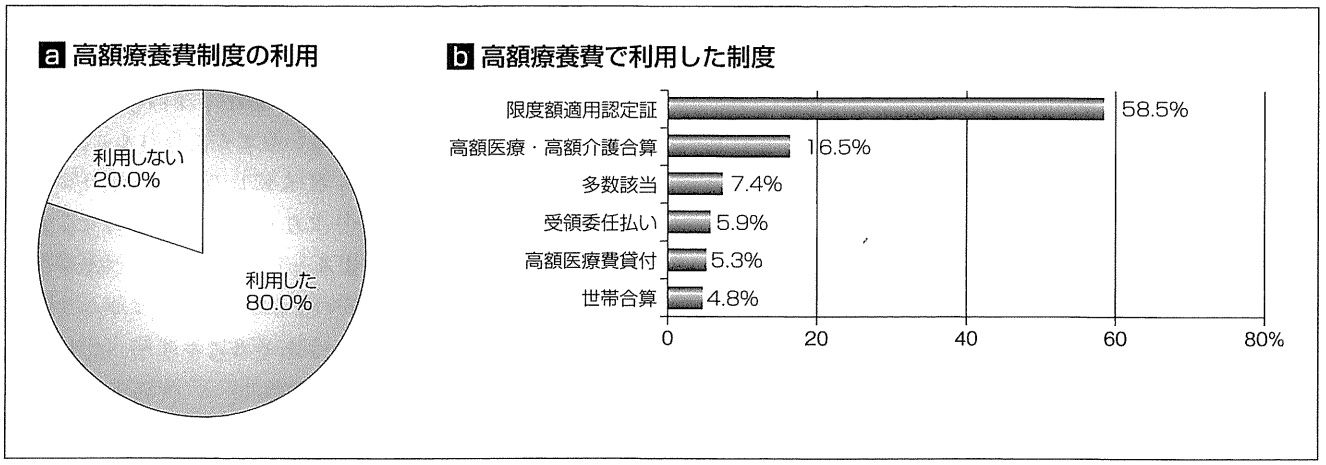

図13　大腸癌患者と高額療養費制度
a：n＝235，b：n＝188
(2010～11年調査)

使用しており，高額医療・高額介護合算も17％に上り，制度の細則についての認識も深まりつつあることがうかがえる。

前述のごとく，高額療養費は2000～2008年の8年間に倍増しており，これは患者の経済的負担が増加していることを意味する。また，この制度は患者が申請してはじめてその対象となる制度であり，利用者が増加していることは，この制度が患者，国民にかなり知られるようになったことを示すものでもある。これには，がん診療連携拠点病院における相談支援センター等で，必要に応じ，この制度が詳しく説明されるようになったことも影響していると思われる。

経済的負担について大腸癌患者の意識をみると，医療費(保険診療)に対しては患者の4分の3が「重い」としている(**図14**)。民間保険の保険料や健康食品・民間療法の費用についても，半数の患者が「重い」と感じている。間接費用は，患者自らの意志で生じる支出が多いが，これもがん罹患に伴う必要な支出ととらえる患者が多く，藁をもつかむ差し迫った心情がうかがわれる。

実際，医療費の支払いは，6割の患者が預貯金の取り崩し，1割の患者は家族・親戚などからの借金で賄っている(**図15**)。今回の調査では，大腸癌患者の平均年齢は64歳であり，定期的な収入は年金のみという患者が少なくないことが影響していると思われる。世帯の過去1年間の税込収入は100～300万未満が患者の3分の1を占め，世帯の貯蓄額は700万円未満が4割弱を占める(**図16**)。

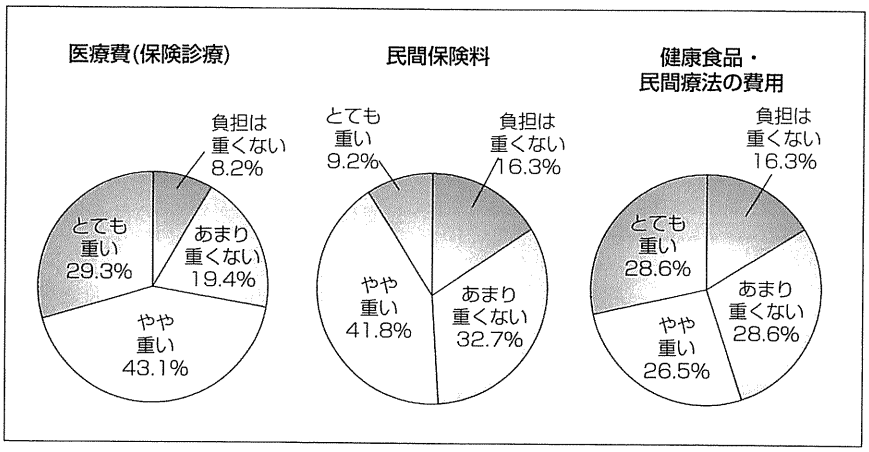

図14　大腸癌患者の経済的負担についての意識
n＝232　(2010～11年調査)

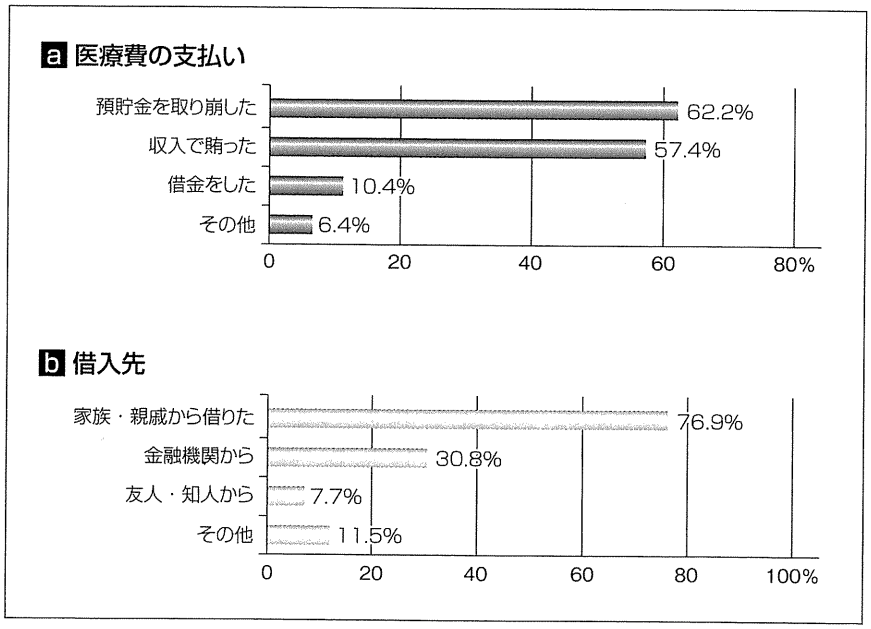

図15　大腸癌患者の医療費支払い状況
a：n＝249(複数回答)，b：n＝26(複数回答)　(2010～11年調査)

経済的理由による治療の変更

国民皆保険の下で，経済的な理由で治療が受けられないことがあってはならないが，最近，高額な治療法を選択できない患者が目立つようになってきた。がん臨床医を対象にした調査(n＝1,176, 臨床経験年数17.8±7.5年)によると，医学的理由ではなく，経済的理由で最適と考えられる治療を変更・中断せざるをえない患者は，1ヵ月に入院で1.5人，外来で1.6人である(**表**)。

経済的な理由による分子標的治療の変更・中止の内訳をみると，無投

薬が37%，予定薬剤の変更が41%，途中中止が13%などである(**図17**)。高額療養費制度等を利用しても，予定した治療を受けられないことは，患者，担当の医療者にとってきわめて深刻な事態である。分子標的薬は高額なことが多いため，変更・中止となることが少なくない。固形腫瘍ではベバシズマブ(アバスチン®)，造血系腫瘍ではリツキシマブ(リツキサン®)，イマチニブ(グリベック®)が多い(**図18**)。

予定した薬物治療がどう変更されたかをみると，例えばベバシズマブの場合，ベバシズマブ＋XELOXがXELOXに，ベバシズマブ＋mFOLFOX6がmFOLFOX6に，ベバシズマブ＋FOLFIRIがFOLFIRIになる，などである。

2011年薬価ベースで，薬剤変更による薬剤費の変化(男，165cm，60kgの患者に対する標準治療)をみると，上記の例では，各46.8万円が22.8万円に(48.6%減)，29.9万円が14.9万円に(49.8%減)，23.2万円が8.2万円に(35.4%減)なる。自己負担額(高額療養費制度等の利用で変化する)でなく，薬価ベースでみると，現行の薬剤費の半額程度が支援されることで，より多くの患者に最適な薬物治療を提供できる可能性があると考えられる(**図19**)。

経済的負担に関する大腸癌患者の要望をみると，抗がん剤をもっと安くしてほしい，がん医療の自己負担割合を他の病気より軽くしてほしい，高額療養費制度の自己負担限度額を引き下げてほしい，長期的負担を軽減する制度にしてほしい，がん医療の経済負担についての正確な情報がほしい，などが多い(**図20**)。長期にわたることが多い薬物治療の負担にあえぐ

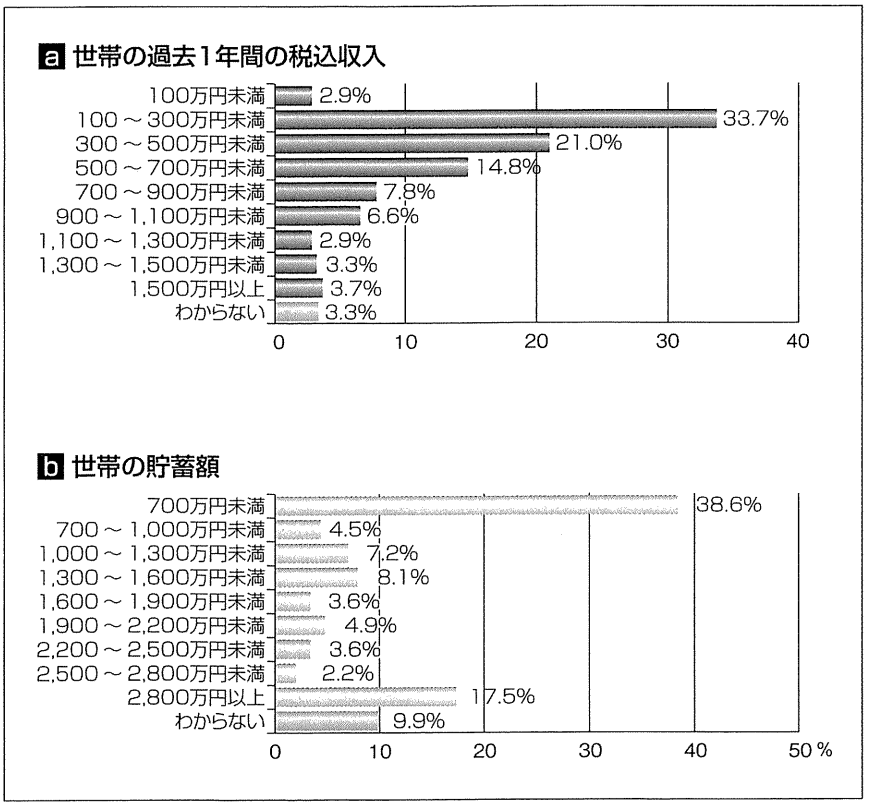

図16　大腸癌患者の家計(平均年齢64.4±10.5歳)
a：n＝243，b：n＝223　(2010～11年調査)

	担当患者数	経済的理由での治療変更・中止	
入院(回答医師 n＝797)	1ヵ月平均	過去1ヵ月間	過去6ヵ月間
	19.7±25.7人	1.5±2.1人	2.3±1.9人
外来(回答医師 n＝864)	1週間平均	過去1ヵ月間	
	39.3±53.9人	1.6±1.8人	

表　経済的理由で治療を変更・中止した患者数
(回答医師：臨床経験年数17.8±7.5年)　(2010～11年調査)

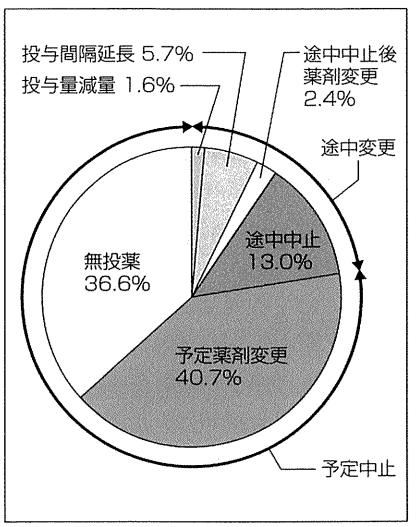

図17　経済的理由による分子標的治療の変更・中止の内訳(固形がん)
n＝123　(2010～11年調査)

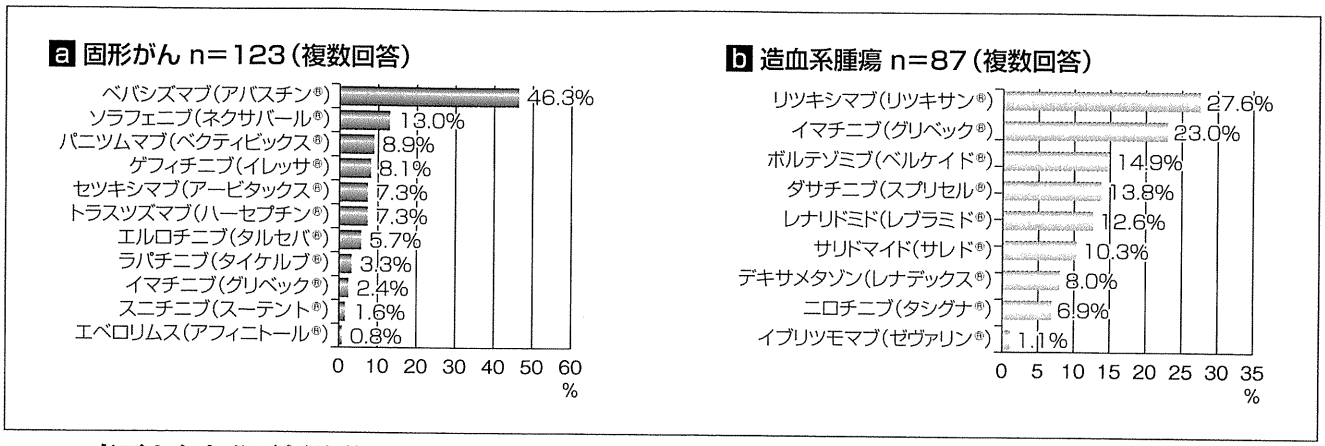

図18　変更された分子標的薬

(2010～11年調査)

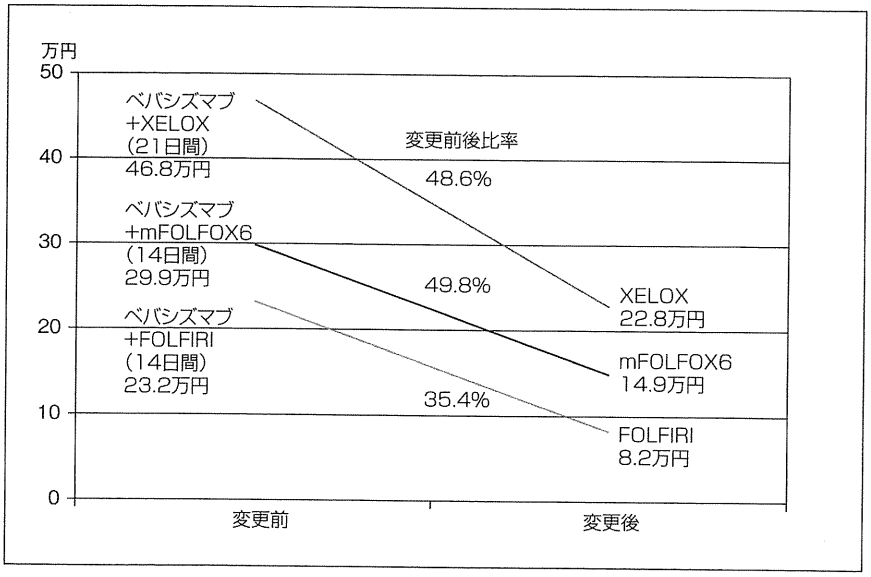

図19　薬剤変更による薬剤費の変化：ベバシズマブ(アバスチン®)

(男，165cm，60kg)　　(2011年薬価ベース)

患者に対応する対策は待ったなしである。加速する技術進歩等に伴って，いわゆるがんの経済難民(経済的理由で十分な治療が受けられない患者)の問題が顕在化する恐れがある。

この対策には，医療現場での配慮，制度運用の工夫，医療制度の改革の3つのレベルがある。医療現場での配慮では，入院にかわる外来治療の推進，在院日数の短縮，検査・投薬の適正化，紹介時の重複検査の回避，安価なジェネリック薬の使用，費用に関する丁寧な説明などである。

制度の運用の工夫では，高額療養費の限度額の引き下げや，ドラッグ・ラグ，ディバイス・ラグの解消，新技術に対する混合診療の拡大(全額自己負担の回避)などである。がんという疾病を特定した患者負担の見直し(負担割合の低減化)も重要な検討課題である。

一人あたり医療費が増加する一方で，国民所得が減少する傾向が長く続く場合，患者負担を過大としないためには，負担割合の引き下げが検討される必要がある。経済的負担が重くなる患者を，すべて高額療養費制度で救済することには限界があるからである。高額療養費は大幅に膨張(2008年度1兆7,130億円)しており，その財源の確保に難渋することになる。

現在，患者全員から外来受診時に定額(100円)を上乗せして，高額療養費の財源にあてる案が浮上しているが，弥縫策のそしりを免れない。今後も高額療養費の急速な増加が想定される以上，受診時定額負担の拡大が避けられず，患者の医療アクセスが制限されるという新たな課題を引き起こしかねない。

必要な医療財源の確保に知恵を絞るとともに，医療費の配分を適正化，合理化することがきわめて重要であ

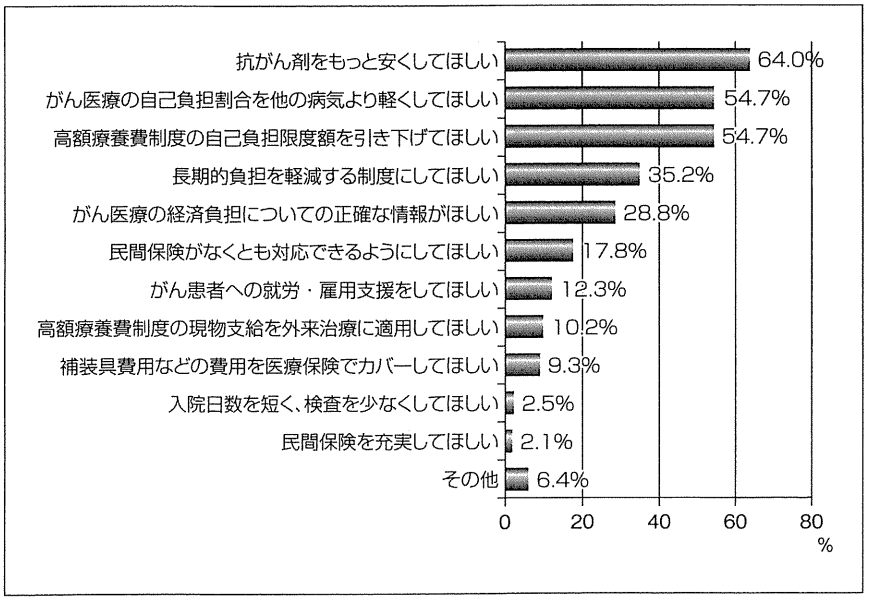

図20　経済的負担に関する大腸癌患者の要望
n＝236（複数回答）　（2010～11年調査）

る。日進月歩の技術革新に対応するには，優先度の高い医療に財源を重点配分するなど，現行の医療保険制度の抜本的な改革が避けられない。医療の優先度設定（一般医療におけるトリアージという考え方）で先行する欧米諸国が参考になる。

おわりに

がん分野の技術進歩は今後ますます加速され，患者の大きな福音となると期待されるが，同時にがん医療の高額化が懸念される。技術進歩をあまねく患者に届けるには，経済的負担を最小化することが欠かせない。ASCO（米国臨床がん学会）が指摘するように，患者負担は治療成績に影響し，費用の検討は質の高いがん医療の重要な要素といえる[2]。がん臨床医は，患者の経済的な負担を洞察し，この負担の軽減に配慮することが重要である。

同時に，がん対策基本法は，国家をあげてがん対策に取り組むことをうたったものであり，これは精神論でなく，財政出動を伴って確実に実効化されなければならない。技術革新に対応できる診療報酬制度の確立を含め，患者負担のあり方を根本的に検討すべき時期に立ち至っていると思われる。

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BRCA1 contributes to transcription-coupled repair of DNA damage through polyubiquitination and degradation of Cockayne syndrome B protein

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***BRCA1* is an important gene involved in susceptibility to breast and ovarian cancer and its product regulates the cellular response to DNA double-strand breaks. Here, we present evidence that BRCA1 also contributes to the transcription-coupled repair (TCR) of ultraviolet (UV) light-induced DNA damage. BRCA1 immediately accumulates at the sites of UV irradiation-mediated damage in cell nuclei in a manner that is fully dependent on both Cockayne syndrome B (CSB) protein and active transcription. Suppression of BRCA1 expression inhibits the TCR of UV lesions and increases the UV sensitivity of cells proficient in TCR. BRCA1 physically interacts with CSB protein. BRCA1 polyubiquitinates CSB and this polyubiquitination and subsequent degradation of CSB occur following UV irradiation, even in the absence of Cockayne syndrome A (CSA) protein. The depletion of BRCA1 expression increases the UV sensitivity of CSA-deficient cells. These results indicate that BRCA1 is involved in TCR and that a BRCA1-dependent polyubiquitination pathway for CSB exists alongside the CSA-dependent pathway to yield more efficient excision repair of lesions on the transcribed DNA strand. (*Cancer Sci* 2011; 102: 1840–1847)**

BRCA1 is an important breast and ovarian cancer susceptibility gene.[1,2] *BRCA1* mutations are rare in sporadic breast and ovarian cancers[3,4] and its expression in these cancers is often reduced,[5] suggesting that BRCA1 plays a role in both hereditary and sporadic carcinogenesis. BRCA1 contains a RING domain at the amino (N)-terminus and two BRCA1 carboxy-terminal (BRCT) domains at the carboxy (C)-terminus. RING domain is an essential component of many ubiquitine E3 ligase. BRCA1 associates with BARD1, which also has a RING domain,[6] and the BRCA1/BARD1 heterodimer has ubiquitin ligase activity.[7–9]

BRCA1 has been implicated in a variety of biological processes, including DNA repair, transcription, chromatin remodeling and centrosome duplication.[10] BRCA1 localizes to nuclear foci during S-phase of the cell cycle.[11] Various mediators of DNA damage such as ultraviolet (UV) irradiation disperse the BRCA1 foci, followed by the reappearance of BRCA1 foci.[12] BRCA1 is phosphorylated in response to UV-induced damage.[13] BRCA1 associates with RNA polymerase II (RNAPII)[14] and mediates the ubiquitination of RNAPII following UV irradiation.[15–17]

The main type of DNA damage induced by UV irradiation is the formation of cyclobutane pyrimidine dimers (CPD) and (6-4) photoproduct adducts. These lesions are removed by nucleotide excision repair (NER). The NER operates via two pathways: transcription-coupled repair (TCR) and global genome repair (GGR). The TCR efficiently removes DNA lesions on the transcribed strands of transcriptionally active genes, whereas the GGR repairs DNA lesions throughout the genome. A stalled RNAPII is presumed to trigger the initiation of TCR in harmony with Cockayne syndrome (CS) proteins. Xeroderma pigmentosum (XP) and CS are rare genetic disorders. Xeroderma pigmentosum is characterized by a high incidence of skin cancer and CS is characterized by photosensitivity and neurodevelopmental abnormalities.[18,19] There are seven genes (*XPA–G*) involved in XP and two genes (*CSA* and *CSB*) involved in CS.[18,20] Mutations in *XPA–G* result in defects in both GGR and TCR, with the exception of *XPC* and *XPE*, which are defective in GGR alone. Patients with CS have defects in TCR, but have functional GGR.

Although BRCA1 is known to function in the repair of DNA double-strand breaks (DSB),[21] there have been several reports suggesting roles for BRCA1 in the excision repair of DNA damage. BRCA1 has been reported to function in NER of oxidative DNA damage[22] and in TCR.[23,24] BRCA1-deficient cells are defective with respect to the preferential removal of oxidative base damage from the transcribed DNA strand.[25] These suggest that BRCA1 participates in the TCR pathway. *BRCA1* mutations or reduced expression of BRCA1 might result in the deficiency of TCR, in addition to DSB repair, and cause an increase in cancer risk and contribute to carcinogenesis.

The aim of the present study was to gain insight into the mechanisms involved in the BRCA1-mediated regulation of TCR. Small, restricted areas of cell nuclei were exposed to UV irradiation using an isopore membrane filter and BRCA1 localization was analyzed. The results showed the immediate, Cockayne syndrome B (CSB)-dependent accumulation of BRCA1 at the UV-irradiated sites. A suggested mechanism for BRCA1 function in TCR is also presented.

Materials and Methods

Plasmid construction. pCMV-Myc-ubiquitin and pcDNA3-HA-BRCA1 have been described previously.[15,26] pcDNA3-HA-BRCA1-I26A was generated by site-directed mutagenesis.

Cell lines and transfections. Saos-2, HEK-293T, XP3BRSV, XP12ROSV, XP4PASV, CS3BESV, UV^{s}1KOSV and HA-CSB/UV^{s}1KOSV cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. HEK-293T cells were transfected with the vectors using Fugene-6 (Roche, Mannheim, Germany).

Localized UV irradiation. Localized UV irradiation was delivered as previously described.[27] Cells were cultured as

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monolayers in 35-mm glass-bottomed dishes (Matsunami Glass, Osaka, Japan), covered with a polycarbonate isopore membrane filter containing pores 3 μm in diameter (Millipore, Billerica, MA, USA), and exposed to 254-nm UV irradiation at a dose of 40 J/m^2.

Immunocytochemistry. Immunocytochemistry was carried out as previously described.[28] An anti-CPD antibody (Medical & Biological Laboratories, Nagoya, Japan) and an anti-BARD1 antibody (H-300; Santa-Cruz Biotechnology, Santa Cruz, CA, USA), a polyclonal anti-BRCA1 antibody specific for residues 397–1080 of BRCA1, or an anti-BRCA1 antibody (C-20; Santa-Cruz Biotechnology) were used.

Small interfering RNA (siRNA). A siRNA targeting BRCA1 was synthesized using a Silencer siRNA construction Kit (Ambion, Austin, TX, USA). The siRNA sequence was 5′-AAGGUUUCAAAGCGCCAGUCA-3′.[29] The Silencer negative control siRNA (Ambion) was used as a negative control. Cells were transfected with siRNA using Lipofectamine RNAiMAX (Invitrogen, Carlsbad, CA, USA).

Immunoprecipitation and western blot. Immunoprecipitation (IP) was carried out as previously described.[28] Total cell lysates were prepared from CS3BESV cells in 1 × SDS sample buffer (2% SDS, 0.67 M 2-Mercaptoethanol, 50 mM Tris–HCl pH 6.8, 12% glycerol, 1% Bromphenol Blue), sonicated and incubated at 95°C for 10 min. Samples were subjected to electrophoresis in SDS-polyacrylamide gels and immunoblotted using anti-BRCA1, anti-CSB (Santa-Cruz Biotechnology), anti-BARD1 or anti-β-actin (Sigma-Aldrich, St. Louis, MO, USA) as indicated.

Colony formation assay. Cells were transfected with control or BRCA1 siRNA. Forty-eight hours after transfection, the cells were replated. Eight hours later, the cells were exposed to UV irradiation and incubated for 10 days. Colonies were stained with 0.3% crystal violet, and the number of colonies was counted and expressed as a percentage of the non-irradiated colonies as a measure of survival.

Analysis of strand-specific DNA repair. The repair of CPD was examined in the 17.9-kb *Kpn*I fragment within the dihydrofolate reductase (DHFR) gene in XP4PASV cells transfected with control or BRCA1 siRNA and irradiated with 8 J/m^2 using a method previously described.[30] Briefly, DNA was extracted, digested with *Kpn*I and treated with T4 endonuclease V, which generates single-strand breaks at CPD sites. The samples were separated by electrophoresis in 0.65% alkaline agarose gels, transferred onto Hybond N$^+$ membranes (Amersham Biosciences, Little Chalfont, Bucks, UK), and hybridized with strand-specific digoxigenin (DIG)-labeled DNA probes. The strand-specific probes were generated by linear PCR in the presence of DIG-11-dUTP using a PCR DIG Probe Synthesis Kit (Roche). Hybridization with DIG-labeled strand-specific probes was detected using a DIG Detection Kit (Roche).

***In vitro* ubiquitination assay.** Reaction mixtures contained 10 mM HEPES (pH 7.6), 0.5 mM EDTA, 5 mM $MgCl_2$, 2 mM NaF, 2 mM ATP, 60 mM KCl, 14 μM ubiquitin (Sigma), 36 nM E1, 12 μM UbcH5c-His, 10 or 20 nM BRCA1-FLAG/BARD1 and 24 nM CSB. The preparation of E1, UbcH5c-His and BRCA1-FLAG/BARD1 has been described previously.[31] CSB was prepared as described previously.[32] After incubation at 37°C for 1 h, CSB modifications were analyzed using western blotting.

Results

BRCA1 accumulates at UV-irradiated sites. To analyze the response of BRCA1 to UV irradiation, cells covered with an isopore membrane filter were irradiated to generate localized UV damage to the cell nuclei.[27,33] Saos-2 cells were exposed to localized UV irradiation and analyzed by co-immunostaining with antibodies against CPD and BRCA1. Five and 30 min after UV irradiation, BRCA1 was distributed as fine nuclear dots that co-localized with CPD (Fig. 1a).

BRCA1 localizes to nuclear foci within a few hours after UV irradiation, which was explained by the response of BRCA1 to the DSB formed at the sites of stalled replication forks in S-phase.[12] However, in asynchronous cells, BRCA1 accumulation at UV-irradiated sites was observed in almost all cells. To exclude the possibility that we were observing BRCA1 accumulation at UV-induced DSB in S-phase, cells were synchronized in G0/G1. BRCA1 clearly accumulated at the UV-irradiated sites in cells at G0/G1 (Fig. S1a,b). In addition, we analyzed whether phosphorylated H2AX (γH2AX), which is rapidly phosphorylated at DSB, was observed at irradiated sites. Even at a higher dose of 100 J/m^2, no γH2AX was detected at UV-irradiated sites 10 min after irradiation (Fig. S1c). These indicate that DSB are not induced immediately after UV irradiation under these experimental conditions. Therefore, it can be concluded that DSB do not induce immediate BRCA1 accumulation after local UV irradiation.

BRCA1 accumulation at UV-irradiated sites is dependent on CSB. To determine whether BRCA1 accumulation at UV-irradiated sites depends on NER factors, the response of BRCA1 to UV irradiation in several NER-deficient cell lines was examined. The cell lines used were: patient-derived *XPG*-deficient XP3BRSV cells, *XPA*-deficient XP12ROSV cells, *XPC*-deficient XP4PASV cells, *CSA*-deficient CS3BESV cells and *CSB*-deficient UV^{s}1KOSV cells. XPC is involved in the damage recognition step of GGR, whereas CSA and CSB function only in TCR. XPA and XPG are required for both GGR and TCR, and function downstream of XPC, CSA and CSB (Fig. 1b). BRCA1 accumulated at UV-irradiated sites in almost all *XPG*-, *XPA*-, *XPC*- and *CSA*-deficient cells as observed in Saos-2 cells, but not in *CSB*-deficient cells (Fig. 1c). Accumulation of BRCA1 at UV-irradiated sites was observed in a stable transfectant of UV^{s}1KOSV cells expressing full-length hemagglutinin (HA)-tagged CSB (HA-CSB/UV^{s}1KOSV).[34] The localization of BRCA1 following irradiation was also examined in mouse embryonic fibroblasts (MEF). BRCA1 accumulated at UV-irradiated sites in *CSA*-deficient (*CSA*−/−) 6L1030 cells, but not in *CSB*-deficient (*XPA*+/− *CSB*−/−) cells (Fig. S2). This suggests that BRCA1 accumulation at UV-irradiated sites is dependent on CSB.

Inhibition of transcription abolishes BRCA1 accumulation at UV-irradiated sites. Cockayne syndrome B plays an important role in the initiation step of TCR through recognition of a stalled RNAPII.[35] To investigate whether the response of BRCA1 is dependent on active transcription, Saos-2 cells were treated with actinomycin D or α-amanitin prior to UV irradiation. Treatment with either chemical completely abolished the accumulation of BRCA1 at the sites of irradiation (Fig. 1d). Although the expression of BRCA1 was slightly decreased by the treatment with actinomycin D, expression of BRCA1 was clearly detected in cells treated with these transcription inhibitors by western blotting (Fig. S3). Thus, the accumulation of BRCA1 at the UV-irradiated sites is dependent on transcription.

Depletion of BRCA1 impairs TCR but not GGR. To determine whether the loss of BRCA1 expression affects TCR, the UV sensitivity of GGR- and TCR-deficient cells transfected with BRCA1 siRNA was examined. In *XPC*-deficient XP4PASV cells, DNA lesions are repaired by TCR, but not by GGR, whereas in *CSB*-deficient UV^{s}1KOSV cells only the GGR pathway is functional. BRCA1 siRNA efficiently suppressed the expression of BRCA1 in these cells (Fig. 2a). Cells were irradiated with varying doses of UV and their ability to form colonies was assessed (Fig. 2b). When BRCA1 expression was reduced, XP4PASV cells were more sensitive to UV irradiation. By contrast, BRCA1 knockdown did not appear to affect the UV sensitivity of UV^{s}1KOSV cells.

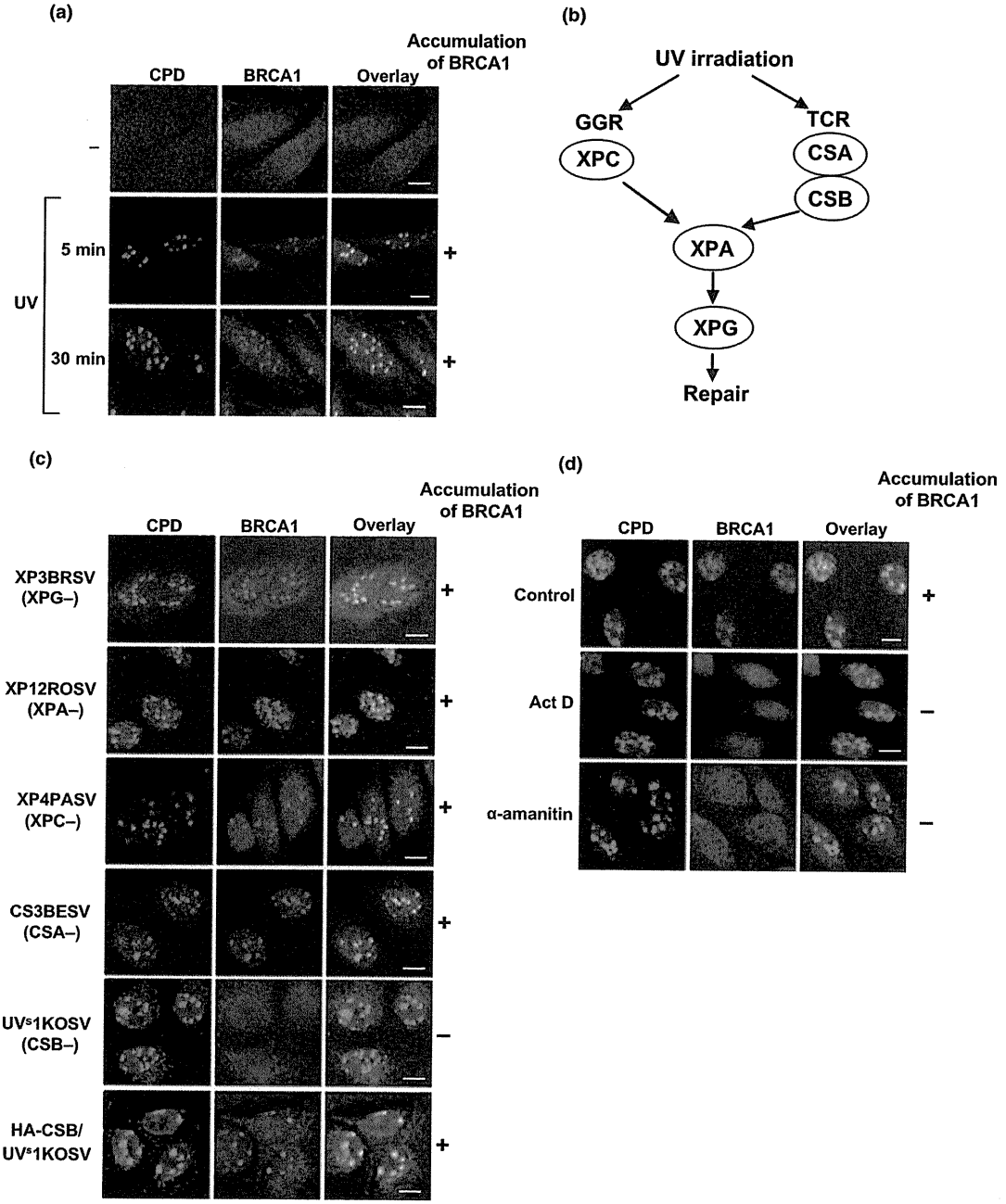

Fig. 1. BRCA1 accumulation at ultraviolet (UV)-irradiated sites is dependent on Cockayne syndrome B (CSB). (a) Saos-2 cells were fixed at the indicated time points after localized UV irradiation and stained with anti-cyclobutane pyrimidine dimers (CPD) and anti-BRCA1 antibodies. (b) Schematic of nucleotide excision repair (NER). (c) XP3BRSV *XPG–/–*, XP12ROSV *XPA–/–*, XP4PASV *XPC–/–*, CS3BESV *CSA–/–*, UV^{5}1KOSV *CSB–/–* and HA-CSB/UV^{5}1KOSV cells were fixed 30 min after UV irradiation and then stained. (d) Saos-2 cells were treated with actinomycin D (Act D) (10 μg/mL) or α-amanitin (100 μg/mL) for 1 h and then exposed to UV irradiation. Scale bars, 10 μm. CSA, Cockayne syndrome A; GGR, global genome repair; TCR, transcription-coupled repair.

Strand-specific DNA probes were also used to examine the removal of CPD from the transcribed and non-transcribed strands of the active DHFR gene in XP4PASV cells transfected with control or BRCA1 siRNA and irradiated. Knockdown of BRCA1 expression reduced the efficiency of CPD removal from the transcribed strand 6 h after UV irradiation (Fig. 2c). This suggests that BRCA1 is important for efficient TCR and mediates resistance to the UV lesion.

Association between BRCA1 and CSB is accompanied by polyubiquitination. To obtain molecular insights into the role of BRCA1 in TCR, the association of BRCA1 with CSB was assessed. HEK-293T cells were UV irradiated and cell extracts were prepared 1 h after exposure. The extracts were then immunoprecipitated with a control IgG or anti-CSB antibody. BRCA1 co-precipitated with CSB (Fig. 3a). In the anti-CSB immune complexes, both BRCA1 and CSB were present as diffuse, slowly migrating bands. Although BARD1 was also detected in anti-CSB immune complexes, it did not show a diffuse pattern. BARD1 accumulated at the UV-irradiated sites (Fig. S4).

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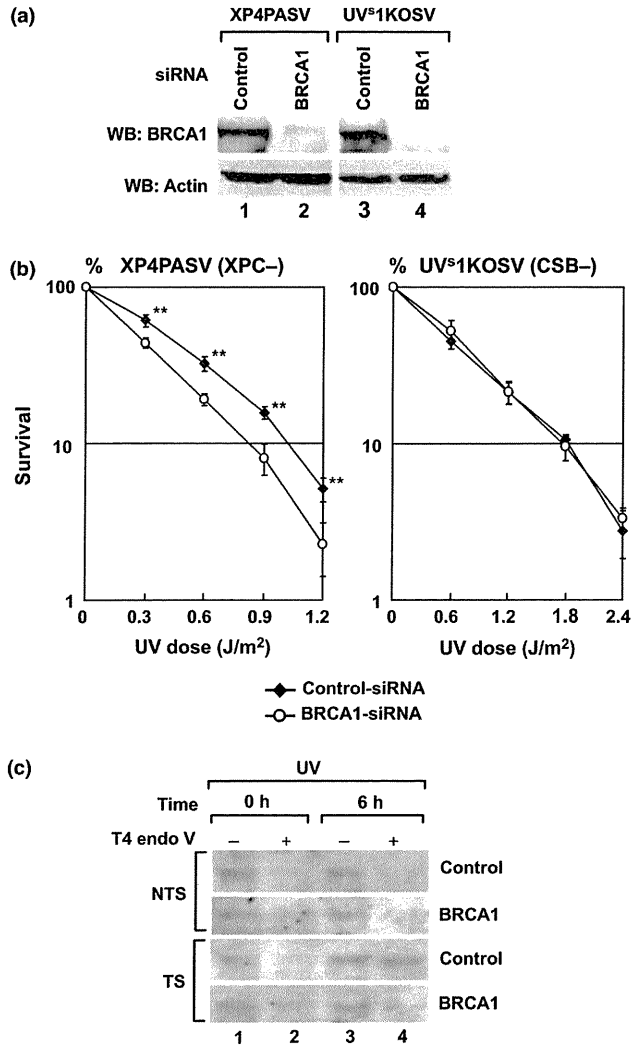

Fig. 2. siRNA knockdown of BRCA1 impairs transcription-coupled repair (TCR). (a) XP4PASV and UV^{s}1KOSV cells were transfected with control or BRCA1 siRNA. Cell lysates analyzed using western blot with anti-BRCA1 and anti-β-actin antibodies. (b) Colony formation assay for XP4PASV and UV^{s}1KOSV cells. XP4PASV and UV^{s}1KOSV cells were transfected with control or BRCA1 siRNA. Data represent the mean ± standard deviations of four independent experiments. $^{**}P < 0.01$ versus the corresponding value for control siRNA. (c) Removal of ultraviolet (UV)-induced CPD from the dihydrofolate reductase (DHFR) fragments in XP4PASV cells immediately or 6 h after UV irradiation. The DHFR fragments were analyzed using strand-specific probes recognizing the transcribed (TS) or non-transcribed (NTS) strand.

Polyubiquitinated proteins show a diffuse pattern on western blots, similar to the behavior observed for BRCA1 and CSB. BRCA1 is ubiquitinated both *in vitro* and *in vivo*, whereas CSB is ubiquitinated *in vitro* only.[36] To determine whether CSB was polyubiquitinated *in vivo*, HEK-293T cells were transfected with a vector expressing a Myc-tagged ubiquitin (Myc-ubiquitin)[15] and then exposed to UV irradiation. Cell lysates were immunoprecipitated with control IgG or anti-Myc antibodies. The slowly migrating form of CSB was clearly precipitated by the anti-Myc antibody (Fig. 3b). Although these slowly migrating bands were observed in non-irradiated cells, the intensity of the bands was enhanced by UV irradiation (Fig. 3c). These indicate that the slowly migrating form of CSB is polyubiquitinated and that UV irradiation increases the polyubiquitination of BRCA1 and CSB.

Polyubiquitinated CSB is processed for proteasomal degradation after UV irradiation. Polyubiquitination is a signal for proteasomal degradation. To determine whether the polyubiquitinated BRCA1 and CSB were targeted for proteasomal degradation following UV irradiation, HEK-293T cells were incubated in the presence or absence of the proteasome inhibitor, MG132, after UV irradiation (Fig. 3d). Treatment with MG132 markedly increased the polyubiquitination of CSB, but not BRCA1. This suggests that CSB is polyubiquitinated and targeted for degradation after UV irradiation, whereas ubiquitination of BRCA1 is unlikely to be coupled to degradation.

BRCA1 polyubiquitinates CSB and is involved in CSA protein-independent resistance to UV irradiation. Cockayne syndrome B is polyubiquitinated *in vitro* by an E3 ubiquitin ligase complex containing CSA and degraded by a proteasomal pathway in a CSA-dependent manner after UV irradiation.[36,37] In contrast, it is reported that CSB expression is downregulated after UV irradiation even in CSA-deficient cells.[38] There might be another pathway for the polyubiquitination and degradation of CSB. Consistent with this expectation, polyubiquitination of CSB was observed in CSA-deficient cells (Fig. 4a). Polyubiquitination of CSB in BRCA1-knockdown cells was significantly lower than that in cells transfected with the control siRNA (Fig. 4b). To test whether the ubiquitin ligase activity of BRCA1 is involved in the polyubiquitination of CSB, HEK-293T cells were transfected with expression vectors for wild-type BRCA1 (HA-BRCA1) or a BRCA1 mutant in which the ubiquitin ligase activity is abolished (HA-BRCA1-I26A).[39,40] In BRCA1-I26A-transfected cells, the polyubiquitination of CSB was markedly lower than that in cells transfected with wild-type BRCA1 (Fig. 4c). These suggest that the ubiquitin ligase activity of BRCA1 is involved in the polyubiquitination of CSB.

Next, ubiquitination assays were performed to determine whether BRCA1 directly ubiquitinates CSB *in vitro*. Purified recombinant CSB protein was incubated with ATP, ubiquitin, E1, UbcH5c and the BRCA1/BARD1 heterodimer and analyzed using western blotting (Fig. 4d). In the complete reaction, polyubiquitinated CSB was observed as slowly migrating diffuse bands and the amount of polyubiquitinated CSB was proportional to the amount of BRCA1/BARD1. This suggests that CSB is a substrate for BRCA1/BARD1.

Next, to assess whether CSB is degraded following UV irradiation in CSA-deficient cells, the amount of CSB was examined in *CSA*-deficient cells following UV irradiation in the presence of cycloheximide (CHX) (Fig. S5a). The amount of CSB protein decreased after UV irradiation in the presence of CHX in CSA-deficient cells. In contrast, CSB protein was not downregulated after UV irradiation in the absence of CHX, as previously reported.[36] The amount of CSB did not alter significantly after treatment with CHX alone (Fig. S5b). Treatment with the proteasome inhibitor together with CHX prevented downregulation of CSB after UV irradiation (Fig. S5c). To examine whether BRCA1 was involved in the downregulation of CSB, CSA-deficient cells were transfected with control or BRCA1 siRNA and the amount of CSB was analyzed after UV irradiation in the presence of CHX. Knockdown of BRCA1 suppressed the downregulation of CSB after UV irradiation in the presence of CHX (Fig. 4e). The amount of BRCA1 in cells transfected with control siRNA decreased following UV irradiation in the presence of CHX, consistent with the report by Hammond-Martel *et al.*[41] These suggest that CSB polyubiquitinated by BRCA1 is degraded via a proteasomal pathway independent of CSA.

Finally, the effect of BRCA1 depletion on the UV sensitivity of *CSA*-deficient cells was analyzed. BRCA1 knockdown

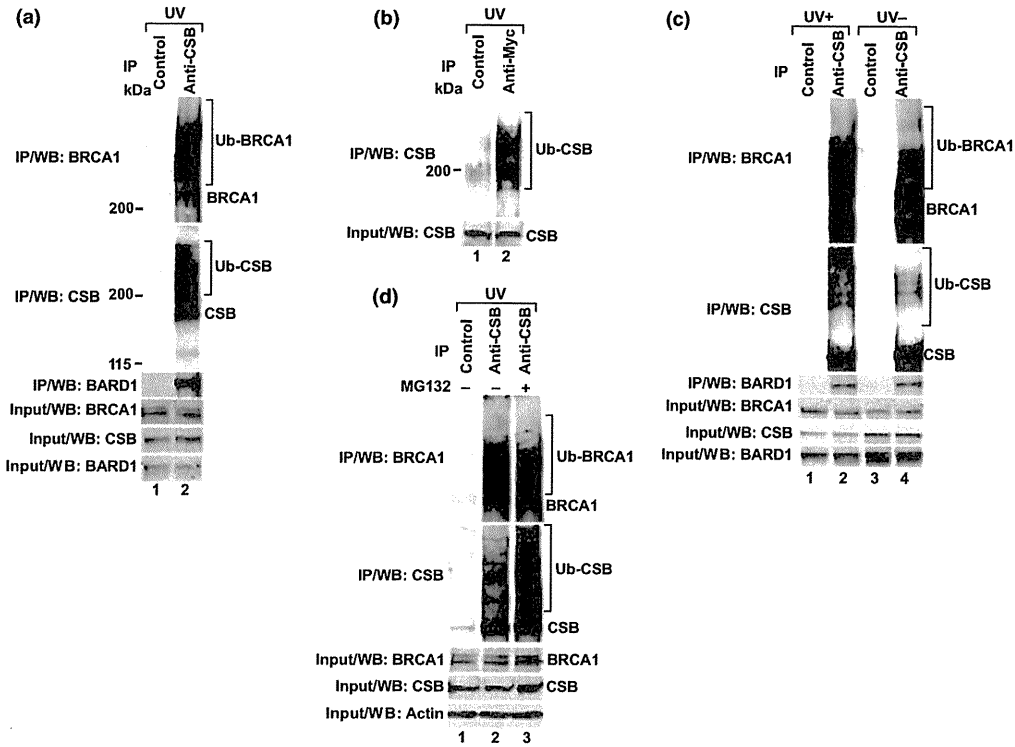

Fig. 3. Cockayne syndrome B (CSB) is associated with BRCA1 and polyubiquitinated for proteasomal degradation after ultraviolet (UV) irradiation. (a) HEK-293T cells were treated with UV irradiation at a dose of 20 J/m^2. One hour after exposure, cell lysates were subjected to immunoprecipitation (IP) with control IgG or anti-CSB antibodies followed by western blotting with anti-BRCA1, anti-CSB or anti-BARD1 antibodies. (b) HEK-293T cells were transfected with Myc-ubiquitin and then UV irradiated. Lysates were subjected to IP using control IgG or anti-Myc antibodies 1 h after UV irradiation. (c) Polyubiquitination of BRCA1 and CSB is enhanced by UV irradiation. (d) CSB polyubiquitination is associated with proteasomal degradation after UV irradiation. HEK-293T cells were treated with or without 50 μM of MG132 after UV irradiation.

increased the UV sensitivity of CSA-deficient cells, supporting a role for BRCA1 in the TCR of UV lesions (Fig. 4f).

Discussion

In the present study we showed that BRCA1 immediately accumulated at locally UV-irradiated sites in a manner that is dependent on CSB and transcription (Fig. 1). Although these are highly suggestive of a role for BRCA1 in TCR, BRCA1 enhances GGR through the transcriptional induction of XPC and DDB2.[42] Therefore, we demonstrated that loss of BRCA1 affects the sensitivity of TCR-proficient and GGR-deficient *XPC*-deficient cells to UV irradiation, but not of GGR-proficient and TCR-deficient *CSB*-deficient cells. Furthermore, the removal of CPD from transcribed strands was suppressed by depletion of BRCA1. Thus, we concluded that BRCA1 is involved in TCR following UV irradiation and increases the survival of cells harboring UV damage.

GFP-tagged CSB protein accumulates in sub-nuclear areas at sites of local UV damage.[43] The amount of CSB protein increases in the chromatin fraction after UV irradiation.[44,45] CSB was responsible for BRCA1 accumulation at UV-irradiated sites. To examine whether BRCA1 moves to chromatin following UV irradiation in a CSB-dependent manner, we fractionated cell lysates from XP4PASV and UV^{s}1KOSV cells into soluble and chromatin-containing fractions (Fig. S6). The amount of CSB protein within the chromatin-containing fractions from XP4PASV cells, increased after UV irradiation. Consistent with Figure 1c, BRCA1 was identified in the chromatin-containing fraction from XP4PASV cells following UV irradiation, but not in that from UV^{s}1KOSV cells.

The CSB-dependent accumulation of BRCA1 at the UV lesions is similar to that seen for other NER factors. Cockayne syndrome A is translocated to the nuclear matrix in an UV- and CSB-dependent manner,[46] and other NER proteins are recruited to TCR sites in a CSB-dependent manner.[44] These suggest that BRCA1 accumulates at UV-irradiated sites and functions in TCR together with other NER factors, and that CSB is an integral factor for recruiting DNA repair factors to TCR sites.

The polyubiquitination of both BRCA1 and CSB was enhanced after UV irradiation. Auto-ubiquitination of BRCA1 enhances its DNA-binding activity.[47] Enhanced polyubiquitination of BRCA1 following UV irradiation might be involved in its function as a DNA repair molecule. However, CSB was polyubiquitinated and processed for proteasomal degradation after UV irradiation. This is consistent with a report that CSB is degraded following UV irradiation.[37] As described above, the amount of CSB increases in the chromatin fraction after UV irradiation. Lake *et al.*[45] reported that the amount of CSB re-appearing in the soluble fraction 7 h after UV irradiation decreases compared with the amount of CSB present before UV irradiation. Cockayne syndrome B might be recruited to the chromatin and then polyubiquitinated for proteasomal degradation after UV irradiation. Since BRCA1 was also recruited to the chromatin fraction after UV irradiation, BRCA1 might ubiquitinate CSB at the chromatin. Phosphorylated RNAPII is also polyubiquitinated by BRCA1 and targeted for proteasomal degradation following UV irradiation.[15,16] BRCA1 might function in TCR through the regulation of protein stability at sites of UV damage.

Depletion of BRCA1 increased UV sensitivity in *CSA*-deficient cells (Fig. 4f), but not in *CSB*-deficient cells (Fig. 2b).

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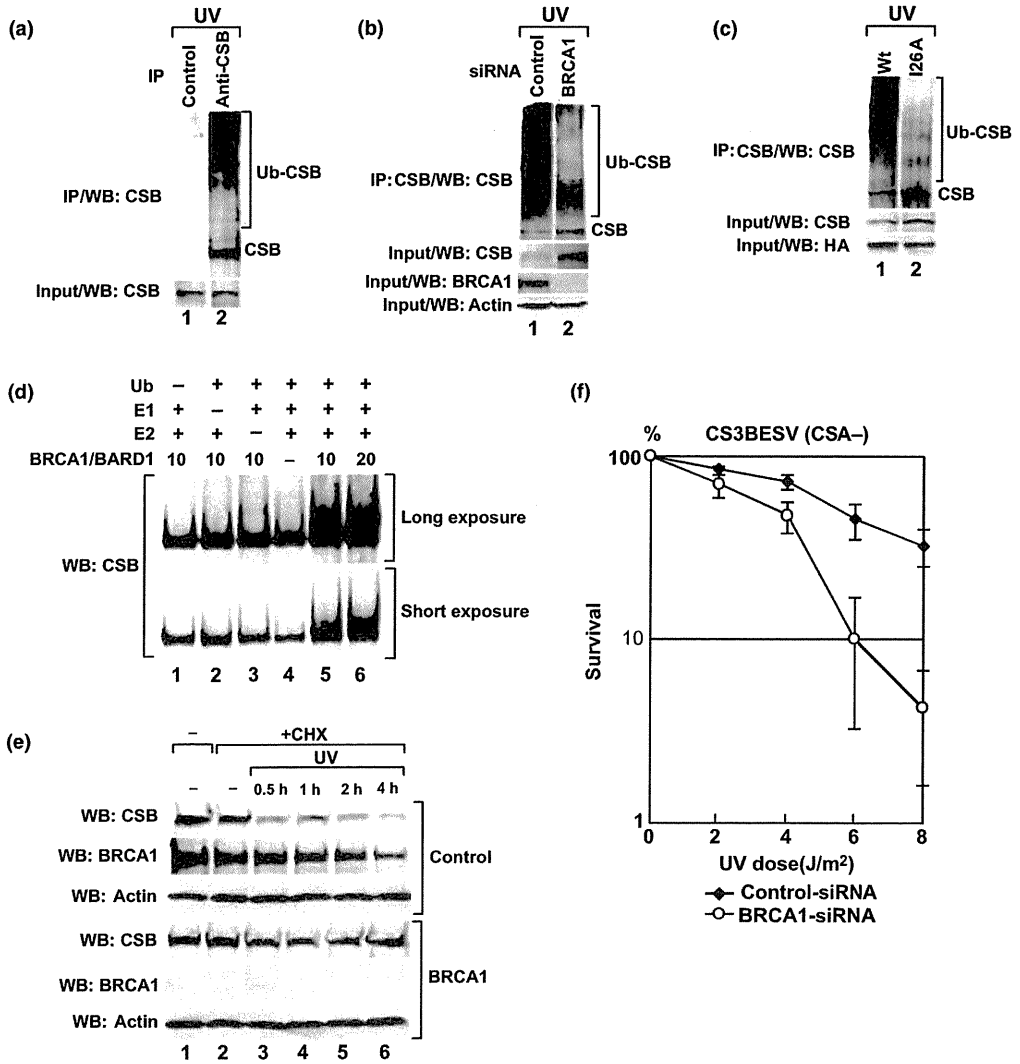

Fig. 4. BRCA1 polyubiquitinates Cockayne syndrome B (CSB) and is involved in the Cockayne syndrome A (CSA)-independent resistance to ultraviolet (UV)-irradiation. (a) CS3BESV cells were treated with UV irradiation. One hour after exposure, cell lysates were subjected to IP. (b) HEK-293T cells were transfected with control or BRCA1 siRNA. One hour after exposure, cell lysates were subjected to immunoprecipitation (IP). (c) HEK-293T cells were transfected with wild-type HA-BRCA1 or HA-BRCA1-I26A. One hour after exposure, cell lysates were subjected to IP. (d) BRCA1 polyubiquitinates CSB *in vitro*. Long and short exposures of the same blot are presented to show that polyubiquitination of CSB is dependent on the amount of BRCA1/BARD1 (10 or 20 nM). (e) CS3BESV cells were transfected with control or BRCA1 siRNA. Cells were pretreated with cycloheximide (CHX) for 1 h and UV irradiated. Cells were incubated with CHX and total cell lysates were prepared at the indicated times for western blot with anti-CSB antibody. (f) Colony formation assay for CS3BESV cells transfected with control or BRCA1 siRNA. The cells were UV irradiatied as indicated. Data represent the mean ± standard deviations of four independent experiments.

This suggests that BRCA1 is involved in TCR for UV damage in a CSB-dependent manner, but independent of CSA. Polyubiquitination of CSB was observed in CSA-deficient cells. Cockayne syndrome B is polyubiquitinated in a BRCA1-dependent manner. Furthermore, CSB was polyubiquitinated by BRCA1/BARD1 *in vitro*, similar to the effect of the CSA complex. Although CSA and BRCA1 might play similar redundant roles in the ubiquitination of CSB, the presence of two independent pathways of CSB polyubiquitination might reflect different roles for CSA and BRCA1 in TCR.

Clinical differences between *CSA*-deficient and *CSB*-deficient patients have not been observed. However, CSA and CSB have different functions in the response to oxidative damage. *CSB*−/− MEF and keratinocytes are hypersensitive to oxidative damage, but *CSA*-deficient cells are not[48]. Cockayne syndrome A functions in the response to oxidative damage, and *CSA*-deficient cell extracts show normal oxidative damage cleavage activity while *CSB*-deficient cell extracts do not.[49] This suggests that downstream pathways that involve CSB exist, one of which might be independent of CSA. Although we identified a function for BRCA1 in TCR of UV lesions in the present study, BRCA1 is also involved in the TCR of oxidative damage[25] and DNA damage induced by ionizing irradiation[23,24]. Therefore, BRCA1 might also be involved in TCR of these DNA damage independent of CSA. Additional studies are needed to gain further understanding of the role played by BRCA1 in TCR pathways.

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Disclosure Statement

The authors have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Immediate BRCA1 accumulation after local ultraviolet (UV) irradiation is not induced by double-strand breaks (DSB).

Fig. S2. Accumulation of BRCA1 at ultraviolet (UV) irradiated sites is dependent on Cockayne syndrome B (CSB).

Fig. S3. Expression of BRCA1 in Saos-2 cells treated with actinomycin D or α-amanitin.

Fig. S4. BARD1 accumulates at sites of ultraviolet (UV) irradiation.

Fig. S5. Cockayne syndrome B (CSB) protein is downregulated after ultraviolet (UV) irradiation in the presence of cycloheximide in Cockayne syndrome A (CSA)-deficient cells.

Fig. S6. Ultraviolet (UV)-irradiation recruits Cockayne syndrome B (CSB) and BRCA1 proteins to the chromatin fraction.

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Burden on Oncologists When Communicating the Discontinuation of Anticancer Treatment

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Objective: Communicating the discontinuation of anticancer treatment to patients is a difficult task. The primary aim of this study was to clarify the level of oncologist-reported burden when communicating about discontinuation of an anticancer treatment. The secondary aims were (i) to identify the sources of burden contributing to their levels and (ii) to explore the useful strategies to alleviate their burden.
Methods: A multicenter nationwide questionnaire survey was conducted on 620 oncologists across Japan (response rate, 67%).
Results: High levels of perceived burden were reported by 47% of respondents, and 17% reported that they sometimes, often or always wanted to stop oncology work because of this burden. There was a significant association between high levels of burden and: a feeling that breaking bad news would deprive the patient of hope; concern that the patient's family would blame the oncologist; concern that the patient may lose self-control; and a feeling that there was not enough time to break the bad news. Strategies perceived to be useful by oncologists included training in how to effectively communicate to patients discontinuation of anticancer treatment, a reduction in total workload to allow sufficient time to break bad news, and development of a multidisciplinary model to facilitate cooperation with other professionals and facilities.
Conclusions: Many oncologists reported high levels of burden relating to communication of discontinuation of anticancer treatment. A specific communication skills training program, sufficient time for communication and development of a multidisciplinary model could help alleviate the burden on oncologists.

Key words: burden – oncologists – communicating

INTRODUCTION

Breaking bad news is a stressful experience for the oncologist (1–6); moreover, it contributes to diminished confidence in communication skills and higher expectations of a negative outcome. The experience of dealing with distressed, angry and reproachful patients is also associated with burnout (7). Previous studies have suggested that oncologist-perceived burden is caused by several factors associated with the patient, the patient's family, the oncologists themselves and the medical environment (8,9). An oncologist's communication style affects the extent of emotional distress felt by the patient and the patient's family (10). The most

difficult conversations involved discussing the discontinuation of curative treatment and admission to a hospice (4); therefore, it is important to clarify the extent of the burden experienced by the oncologist when communicating the discontinuation of anticancer treatment.

Many studies have been conducted to clarify patients' preferences and experiences in receiving bad news in oncology settings (11–14), and several clinical guidelines and expert recommendations have been published (1,15,16). Moreover, recent intervention trials have demonstrated that structured communication skills training can improve physicians' skills in breaking bad news (17–19).

Despite the existence of many experience-based recommendations and studies into the psychological effects on patients and their families, to our knowledge, only a few studies have explored the extent of the burden on oncologists when communicating the discontinuation of anticancer treatment. Therefore, the aims of the present study were to: (i) clarify the level of oncologist-perceived burden when communicating the discontinuation of anticancer treatment to patients; (ii) identify factors contributing to this burden; and (iii) explore potentially useful strategies to alleviate oncologist-perceived burden.

PATIENTS AND METHODS

Subjects

The present study was a cross-sectional anonymous multicenter nationwide survey of oncologists in cancer centers across Japan. Questionnaires were mailed to 620 eligible oncologists in February 2007 and again 2 months later to those oncologists who had not yet responded. If the oncologists did not want to participate in the survey, we requested that they return the questionnaire without replying to any of the questions. The participating institutions were 12 cancer centers selected from the 15 cancer centers that make up the Japanese Association of Clinical Cancer Centers.

We recognized potential sampling bias with this method, but decided to use convenient institutions because we felt that the risk of sampling bias would be minimized by a large number of participants.

Eligibility criteria for the participants were as follows: (i) oncologists specializing in gastroenterology, respiratory medicine, breast oncology, hematology, medical oncology, urology, gynecology, otolaryngology, orthopedics, pediatrics, neurosurgery or dermatology; and (ii) the oncologist's name had to appear on his/her medical facility's website. The website of all Japanese cancer centers shows the complete list of all physicians in that center. We regarded the completion and return of the questionnaire as consent to participate in the study. The institutional review board of the principal investigator confirmed the study's ethical and scientific validity.

Questionnaire

A questionnaire was developed based on a review of the literature (2,3,8,9) and discussions among the authors. Content validity was assessed by full agreement of the authors, and face validity was confirmed by a pilot test of 20 potential participants.

As background data, oncologists reported their age, gender, clinical experience in oncology, specialty, previous experience with formal communication skills training, attitudes toward disease and prognosis disclosure for terminally ill patients, and the number of patients to whom they would usually communicate the discontinuation of anticancer treatment annually.

The primary endpoint was oncologist-perceived burden imposed by communicating the discontinuation of anticancer treatment to patients. Given the lack of existing validated instruments, the following outcome parameters were developed by the authors. First, the level of oncologist-perceived burden was evaluated by the question, 'What level of burden do you feel when you communicate with patients about discontinuation of anticancer treatment?' Answers to this question were rated on a five-point scale ranging from 1 (I do not feel any burden at all) to 5 (I feel a heavy burden). In addition, we investigated the impact of the burden on motivation to continue working in oncology by asking oncologists, 'How often do you feel some level of desire to stop oncology work due to this burden'. Again, answers were rated on a five-point scale ranging from 1 (not at all) to 5 (always).

We extracted 20 potential sources of burden from the literature (8,9) and questioned oncologists on their level of perceived burden relating to each of these sources. Oncologists were requested to rate their degree of burden on a five-point Likert-type scale ranging from 1 (I do not feel any burden) to 5 (I feel a heavy burden).

In addition, we developed a list of 14 potentially useful strategies to alleviate oncologists' perceived burden derived from a previous report (20) and from a qualitative study using in-depth interviews with three oncologists. The oncologists were requested to rate their level of agreement with each of these strategies on a six-point Likert-type scale ranging from 1 (not necessary) to 6 (absolutely necessary).

Statistical Analyses

For comparisons, respondents were classified into two groups: oncologists who rated themselves as 'heavily burdened' or 'burdened' (high-level burden) and then all other oncologists (low-level burden). This cut-off point was selected on the basis of the actual distribution of the data and enabled the entire sample to be divided into two equal-sized groups for comparison.

To explore the determinants of levels of oncologist-reported burden, we screened 7 background variables and 20 sources of burden. Univariate analyses were performed using Student's t-test or the χ^2 test, as appropriate. To assess the

results in 20 comparisons, the P value necessary for statistical significance was defined as 0.0025 (0.05/20) using the Bonferroni correction. Multiple logistic regression analyses were then performed using a forward elimination procedure. All potential predictors with statistical significance as ascertained by the univariate analyses were included as independent variables in multiple logistic regression analyses. All analyses were performed using SPSS version 11.0.

RESULTS

Of the 620 questionnaires mailed to oncologists, 10 were undeliverable because of incorrect addresses and 416 oncologists returned questionnaires, resulting in a response rate of 67%. Of the questionnaires returned, 3 were excluded due to missing data in primary endpoints and 19 were returned without any of the questions being answered. Thus, a total of 394 responses were analyzed, giving an effective response rate of 67% (394/591). The oncologists' characteristics are summarized in Table 1.

Overall levels of oncologist-reported burden relating to communication of the discontinuation of anticancer treatment were: heavily burdened, 13%; burdened, 34%; slightly burdened, 37%; not particularly burdened, 13%; or not burdened at all, 1.3% (Table 2). Clinical oncologists rated their level of desire to stop oncology work because of this burden as: not at all, 55% ($n = 218$); rarely, 26% ($n = 106$); sometimes, 11% ($n = 45$); often, 5.3% ($n = 21$); or always, 1.0% ($n = 4$).

The oncologists' ratings of the 20 potential sources of burden relating to the communication of discontinuation of anticancer treatment are given in Table 3. More than 20% of respondents reported feeling 'heavily burdened' or 'burdened' by the following factors: insufficient time to break bad news; feeling that breaking bad news will deprive the patient of hope; the possibility that the breaking of bad news is interrupted by other tasks; concern that the patient may lose self-control; opposition from the patient's family to breaking bad news to the patient; the fact that evidence from a certain group is not applicable to every patient; and, finally, an inability to answer philosophical questions regarding death and the value of life.

Univariate analysis (Table 4) showed that oncologists with high-level burden were significantly more likely to report the following concerns: feeling that breaking bad news will deprive the patient of hope; concern that the oncologist may be blamed by the patient's family; concern that the patient may lose self-control; insufficient time to break bad news; possibility that the time for breaking bad news is interrupted by other tasks; opposition from the patient's family to breaking bad news to the patient; evidence from a certain group is not applicable to every patient; an inability to answer philosophical questions regarding death and the value of life; feeling a sense of guilt because oncologists cannot provide adequate treatment; concern that the oncologist may be criticized by the patient; scientific evidence is not always predictable or reproducible; opposition from patients to breaking bad news to their families; fear of talking to patients whom the oncologist do not know very well; lack of confidence in oncological medical skills; uneasiness in changing roles from curing patients to caring for patients; and a concern that an objective stance cannot be maintained if the oncologist becomes too intimate with the patient.

Multiple logistic regression analysis (Table 4) revealed that independent determinants of high-level burden were: feeling that breaking bad news will deprive the patient of hope; concern that the oncologist may be blamed by the patient's family; concern that the patient may lose self-control; and insufficient time to break bad news. Seven backgrounds of the oncologist, including age, specialty, attitudes toward disease and prognosis disclosure for terminally ill patients, oncology experience, previous experience with

Table 1. Background of respondent oncologists

Age (years)	
Median	43
Inter-quartile range	37–50
Male gender [no. (%)]	371 (91)
Oncology experience (years)	
Median	15
Inter-quartile range	8–20
Number of communications concerning discontinuation of anticancer treatment annually	
Median	8
Inter-quartile range	3–15
Attitudes toward disease and prognosis disclosure for terminally ill patients[a] [no. (%)]	
Routinely, without patient's request	55 (14)
If necessary, without patient's request	234 (59)
If necessary, and if the patient explicitly asks	78 (19)
Routinely, and if the patient explicitly asks	21 (5.3)
Specialty[a] [no. (%)]	
Gastroenterology	116 (30)
Respiratory medicine	50 (13)
Breast oncology	42 (10)
Hematology, medical oncology	42 (10)
Urology	32 (8.3)
Gynecology	30 (7.8)
Otolaryngology	24 (6.2)
Orthopedics	19 (4.9)
Neurosurgery	12 (3.1)
Pediatrics	13 (3.3)
Dermatology	5 (1.3)
Received formal training in breaking bad news [no. (%)]	59 (16.5)

[a]Percentages do not add up to 100% because of missing data.

formal communication skills training, or number of communications concerning discontinuation of anticancer treatment annually, are not the determinants of levels of oncologist-reported burden.

Strategies to relieve oncologist-reported burden when communicating the discontinuation of anticancer treatment were also investigated. Table 5 lists the percentage of oncologists who agreed with each of the 14 strategies suggested to alleviate oncologists' perceived burden. More than 20% of respondents considered the following strategies to alleviate oncologist-reported burden as 'absolutely necessary': that an inpatient hospice is readily available and that patient information is exchanged smoothly among facilities; quiet and private rooms are available for breaking bad news; after breaking bad news, a nurse, psychologist or medical social worker is available to provide emotional support; and a reduction in oncologists' total workload to give them sufficient time to break bad news.

Table 2. Levels of oncologist-reported burden when communicating discontinuation of anticancer treatment

	No. (%)
Heavily burdened	53 (13)
Burdened	136 (34)
Slightly burdened	147 (37)
Not particularly burdened	53 (13)
Not burdened at all	5 (1.3)

DISCUSSION

To the best of our knowledge, this is the first large multicenter nationwide survey to investigate oncologist-reported burden when communicating the discontinuation of anticancer treatment. The first important finding of the present study was the demonstration of the oncologist-reported burden when

Table 3. Sources of oncologist-reported burden when communicating discontinuation of anticancer treatment

	'Not burdened at all', no. (%)	'Not particularly burdened', no. (%)	'Slightly burdened', no. (%)	'Burdened', no. (%)	'Heavily burdened', no. (%)
Insufficient time to break bad news	12 (3.1)	61 (15)	90 (22)	151 (36)	82 (20)
Feeling that breaking bad news will deprive the patient of hope	12 (3.1)	34 (8.7)	152 (37)	135 (33)	63 (15)
Possibility that the time for breaking bad news is interrupted by other tasks	18 (4.6)	86 (21)	102 (25)	120 (29)	71 (17)
Concern that the patient may lose self-control	16 (4.1)	83 (21)	163 (39)	108 (26)	25 (6.0)
Opposition from family members to breaking bad news to the patient	39 (9.9)	96 (24)	134 (32)	91 (22)	36 (8.7)
Evidence from a certain group does not always apply to the patient	43 (10)	122 (31)	133 (32)	70 (17)	28 (6.7)
The oncologist is unable to answer philosophical questions regarding death and the value of life	37 (9.5)	122 (31)	140 (34)	74 (18)	21 (5.0)
Concern that the oncologist may be blamed by the patient's family	73 (18)	141 (35)	104 (25)	63 (15)	15 (3.6)
Feeling a sense of guilt because oncologists cannot provide effective anticancer treatment	83 (21)	140 (35)	102 (25)	56 (14)	14 (3.4)
Opposition from patients to breaking bad news to their families	70 (17)	171 (43)	87 (21)	47 (11)	19 (4.6)
Concern that the oncologist may be criticized by the patient	75 (19)	149 (37)	107 (26)	56 (14)	9 (2.2)
Fear of talking to patients whom oncologist does not know very well	84 (21)	138 (35)	108 (26)	54 (13)	10 (2.4)
Scientific evidence is not always predictable or reproducible	43 (10)	122 (31)	133 (32)	70 (17)	28 (6.7)
Lack of confidence in oncological medical skills	63 (16)	172 (43)	106 (26)	49 (12)	5 (1.2)
Concern that the oncologist does not have the latest knowledge	80 (20)	179 (45)	97 (23)	36 (8.7)	2 (0.5)
Uneasiness in changing roles from curing patients to caring for patients	111 (28)	176 (44)	68 (16)	34 (8.2)	4 (1.0)
Concern that oncologists cannot answer all knowledge-based questions posed by the patient	94 (24)	186 (47)	81 (20)	29 (7.0)	3 (0.7)
Oncologists fear their own illness and death	122 (31)	178 (45)	62 (15)	26 (6.3)	4 (1.0)
Concern that an objective stance cannot be maintained if the oncologist becomes too intimate with the patient	89 (22)	195 (49)	85 (20)	24 (5.8)	3 (0.7)
Fear that oncologists themselves may become very emotionally involved, such as expressing anger or sadness	107 (27)	209 (53)	59 (14)	18 (4.3)	0 (0)

Percentages do not add up to 100% due to missing data.

Table 4. Determinants of oncologist-reported burden when communicating discontinuation of anticancer treatment

	Univariate analyses			Multivariate analyses	
	Low level ($n = 206$)	High level ($n = 190$)	*P* value	Odds ratio (95% CI)	*P* value
Feeling that breaking bad news will deprive the patient of hope	3.1 ± 0.9	3.8 ± 0.8	<0.01	1.8 (1.4–2.5)	<0.01
Concern that the oncologist may be blamed by the patient's family	2.1 ± 0.8	2.8 ± 1.1	<0.01	1.5 (1.2–1.9)	<0.01
Concern that the patient may lose self-control	2.8 ± 0.8	3.4 ± 0.9	<0.01	1.4 (1.1–1.9)	<0.01
Insufficient time to break bad news	3.3 ± 1.0	3.8 ± 0.9	<0.01	1.2 (0.99–1.6)	0.049
Possibility that the time for breaking bad news is interrupted by other tasks	3.1 ± 1.0	3.5 ± 1.1	<0.01		
Opposition from family members to breaking bad news to the patient	2.7 ± 1.0	3.2 ± 1.1	<0.01		
Evidence from a certain group does not always apply to every patient	2.6 ± 0.9	3.0 ± 1.1	<0.01		
The oncologist is unable to answer philosophical questions regarding death and the value of life	2.5 ± 0.8	3.0 ± 1.0	<0.01		
Feeling a sense of guilt because oncologists cannot provide effective anticancer treatment	2.1 ± 0.9	2.7 ± 1.1	<0.01		
Concern that the oncologist may be criticized by the patient	2.1 ± 0.8	2.7 ± 1.0	<0.01		
Scientific evidence is not always predictable or reproducible	2.3 ± 0.8	2.7 ± 1.0	<0.01		
Opposition from patients to breaking bad news to their families	2.2 ± 0.8	2.6 ± 1.2	<0.01		
Fear of talking to patients whom the oncologist does not know very well	2.2 ± 0.9	2.5 ± 1.1	<0.01		
Lack of confidence in oncological skills	2.2 ± 0.8	2.5 ± 0.9	<0.01		
Uneasiness in changing roles from curing patients to caring for patients	1.9 ± 0.8	2.3 ± 0.9	<0.01		
Concern that an objective stance cannot be maintained if the oncologist becomes too intimate with the patient	1.9 ± 0.7	2.2 ± 0.8	<0.01		
Concern that the oncologist does not have the latest knowledge	2.1 ± 0.8	2.2 ± 0.9	0.24		
Fear that the oncologist may become very emotionally involved, such as expressing anger or sadness	1.9 ± 0.6	2.0 ± 0.8	0.24		
Concern that the oncologist cannot answer all knowledge-based questions posed by the patient	2.0 ± 0.8	2.2 ± 0.9	0.34		
Fear of the oncologists' own illness and death	1.9 ± 0.7	2.0 ± 1.0	0.78		

Oncologists who rated their burden level as heavily burdened or burdened (high-level group) are compared as a single group against all others (low-level group). Multiple logistic regression analyses used the high-level burden group as the dependent variable. Each condition was rated on a scale of 1 (do not feel any burdened) to 5 (feel heavily burdened).

communicating the discontinuation of anticancer treatment to patients. Of the oncologists surveyed, 47% reported high levels of burden when communicating the discontinuation of anticancer treatment. Moreover, 17% of the oncologists surveyed reported that they sometimes, often or always want to stop oncology work because of this burden. Multiple studies have revealed that a major contributor to physicians' burnout is communication with patients and families (21–26). The present study confirms that communication with patients and families is a major source of oncologists' work-related stress. In particular, the present study highlights that communicating the discontinuation of anticancer treatment can be a heavy burden for oncologists and that it is urgent that strategies are developed to alleviate this burden.

The present study also evaluated oncologists' opinions regarding the strategies likely to be effective in reducing this burden. The strategies perceived to be potentially effective included: ready availability of an inpatient hospice and smooth exchange of patient information among facilities; availability of quiet and private rooms for the breaking of bad news; the provision of emotional support from a nurse, psychologist or medical social worker after the patient has received the bad news; and a reduction in oncologists' total workload to give them sufficient time to break the bad news.

Moreover, multiple logistic regression analyses revealed that independent determinants of high-level burden were: a feeling that breaking bad news will deprive the patient of hope; concern that the oncologist may be blamed by the patient's family; concern that the patient may lose self-control; and insufficient time to break bad news.

These results reveal that there are three main areas that, if addressed, could significantly alleviate oncologist-reported burden: (i) improving oncologists' communication skills; (ii) allowing sufficient time for communication with patients and