Survival in young adults with cancer shows little change across decades. Why is that, and how can the disease be pushed back?

# In Their Prime, And Dying of Cancer

**THE NUMBERS STARED BETHANY** Hartung bleakly in the face. Cancer survival rates in older adults and children had inched up an average of 1% or 2% each year over 2 decades, the graph showed. But for teenagers and young adults like her, the prospects for survival had barely budged.

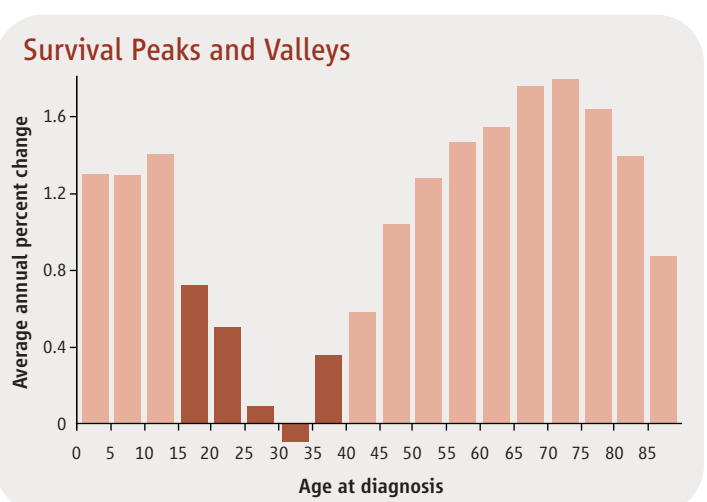
Remembering the moment she came across those statistics, "I was just kind of amazed," said Hartung, 21, in a telephone conversation from her family's home outside Portland, Oregon, 5 days before she died of leukemia. She had endured two relapses and nearly 3 years of grueling treatment, including a bone marrow transplant. When that failed to help, she was offered a spot in an experimental phase I study of a toxic therapy that she believed had little chance of beating back the disease. Hartung declined. "It was pretty much an easy decision," she said. Instead, she entered hospice care at home and died on 24 June, 2 weeks before her 22nd birthday.

According to data on age and risk, Hartung's chances would have been far better had she been diagnosed at 9 instead of at 19. Reversing her particular disease, acute lymphoblastic leukemia (ALL), is one of the great cancer success stories of the 20th century. In 1970, roughly 80% of children with the disease died; today, 80% will survive. But that heartening figure takes a dive in older teenagers and young adults, for whom 5-year survival hovers around 50%. No one knows exactly why.

The mystery extends well beyond ALL. Breast cancer, colon cancer, bone tumors, certain lymphomas, and Ewing sarcoma, which attacks bone and soft tissue, are all likelier to kill 15- to 39-year-olds than those in many other age groups. Adolescents and young adults (AYAs) with cancer once had better prospects than children and older adults. But their survival rates have been virtually frozen since about 1975.

The possible explanations are many and much debated. One is that therapies are not being designed for them because AYAs are poorly represented in clinical trials. Diagnosis often comes later, perhaps because of their aura of invincibility. In the United States, this cohort is less likely than other groups to have health insurance. Finally, their treatments may not be aggressive enough.

Some oncologists offer an altogether different explanation. "My own personal belief is that one part




**Grim news, for some.** From 1975 to 1999, the chance of surviving cancer for 5 years slowly improved in older adults and children but not for those in between.

CREDIT: KEVIN LAUBACHER/GETTY IMAGES; SOURCE: SEER

of this must be the distinctive biologies" of the patients or their tumors, says Michael Caligiuri, director of the Ohio State University Comprehensive Cancer Center in Columbus. He admits that laboratory proof is lacking, however.

Efforts to address this controversial idea are heating up. Researchers are beginning to assemble tissue banks dedicated to young adult tumors and looking for clues in the literature. This fall, after years of planning, one of the first clinical trials limited to 16- to 29-year-olds will examine the age group's lagging survival in ALL. And in the past 2 years, the Lance Armstrong Foundation in Austin, Texas, has poured nearly $2 million into the field and begun to reverse what is seen as years of neglect of AYA patients, whose U.S. ranks grow by nearly 70,000 each year.

"You see two patients who come in with what the pathologist tells you is the same disease, and you see drastically different outcomes" depending on age, says Caligiuri. "The onus is upon us to sort it out."

**Fighter.** Bethany Hartung (*center*), 21, celebrates Christmas last year with her older sisters. She died in June of leukemia.

CREDIT: PAM KRAMER

### Knowledge gulf

Assembling the jigsaw puzzle will demand an alliance that extends across the boundaries of age—a rarity in medicine. "Biology doesn't change on a dime on the day of the 18th birthday," says Karen Albritton, who directs the Adolescent and Young Adult Oncology Program at Dana-Farber Cancer Institute in Boston. But the health-care and biomedical research enterprises act as though it does.

Albritton has experienced this cultural divide firsthand. From her residency days, she knew she did not want to choose between treating children or adults. But she recalls doctors telling her that working in both camps "would be combining things that don't combine."

That thinking is reflected in the paucity of data on the AYA crowd. In children, "we have great tissue banking for leukemia," says Leonard Sender, who directs adolescent and young adult cancer programs at Children's Hospital of Orange County and at the University of California, Irvine. "As soon as you go to 18, 19, 21," he says, the samples are "totally falling off."

Clinical trials, meanwhile, rarely include older teenagers and young adults. Roughly 30% to 50% of child cancer patients under 15 participate in clinical trials, whereas for adolescents and young adults the number hovers around 1% or 2%. (The comparable figure for adults 40 and up is about 3% to 5%.) Some trials have age limits that keep older teens from enrolling. Others are based at children's hospitals, where few young adults are treated.

Take Ewing sarcoma, which strikes bone and soft tissue. One large Ewing's trial of a new chemotherapy combination published in 2003 and led by oncologist Holcombe Grier at Children's Hospital Boston included 518 patients. Fifty were 18 or older. More than double that number were under 10. The average age at diagnosis with Ewing's, however, is about 15.

"We don't really have a focus on whether the treatments that we know work in children work in older age groups," says Australian oncologist David Thomas. Thomas directs the adolescent and young adult cancer program at the Peter MacCallum Cancer Centre in Melbourne, Australia, as well as the hospital's sarcoma genomics and genetics laboratory. Frustration shades his words as he talks about how poorly AYA cancers are understood. Even the most rigorously designed clinical trial will not detect AYA-specific differences in drug response or tumor biology, says Thomas, if only a tenth of participants are from this age group.

Data on young adults are also scarce because relatively few trials focus on the predominant tumors in this group: sarcomas, melanomas, thyroid cancer, gonadal tumors such as testicular cancer, and lymphomas. Some melanoma trials, which Sender notes already include few patients under 30, are ramping down because of tight federal budgets.

Before researchers began studying AYA patients with cancer, there was little awareness that survival rates were stagnant. Some studies did suggest that young adults with certain cancers, like sarcomas, were at a survival disadvantage compared with children—but it wasn't clear why. Albritton notes that she had treated older patients whose oncologists, unaccustomed to a cancer such as Ewing sarcoma that's more familiar to pediatricians, sometimes omitted chemotherapy. And a 2003 German study suggested that AYAs with Ewing's fare better in pediatric centers. Grier's clinical trial underscored that biology might also be key. Although the focus of Grier's trial was a new chemotherapy regimen in Ewing sarcoma, it contained some startling statistics. Treatment was standardized, yet the 5-year survival rate for children under 10 was 70%, compared with 60% for 10- to 17-year-olds and 44% for those 18 years and older. "We don't have any understanding" of why this occurs, says Albritton.

### Behind the numbers

Several forces galvanized the cancer research community to dig deeper into AYA cancers. The first was a persistent campaign by W. Archie Bleyer. Trained as a pediatric oncologist, Bleyer worked for many years at the University of Texas M. D. Anderson Cancer Center in Houston before moving to St. Charles Medical Center in Bend, Oregon. Bleyer compiled and publicized the stagnant AYA survival statistics that astonished oncologists. Says Caligiuri of Ohio State University: "You look at [the numbers] and go, 'Oh my god, what is wrong here?' "

A second factor was an expanding advocacy community, led by the Lance Armstrong Foundation. Founded by the Tour de France champion who beat metastatic testicular cancer, the foundation joined with the National Cancer Institute to issue a set of "research and care imperatives" in 2006 and in May published a strategic plan for boosting AYA survival. The Lance Armstrong effort, called the LIVESTRONG Young Adult Alliance, is now led by 39-year-old Ewing sarcoma survivor Heidi Adams, who runs the advocacy group Planet Cancer, and oncologist Brandon Hayes-Lattin of Oregon





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Health and Science University in Portland, who exhausted his arsenal trying to save Hartung. It will hold its second annual meeting in Austin in November.

Albritton, Bleyer, and many others are donating their time to one of its first projects, a literature search for clues about tumor biology. For example, a mention of young adults in a paper might prompt a call to the authors for additional data. "If there was a big breast cancer study but it lumped all the ages together, we go back to authors and say, 'Can you look at this by age?' " says Albritton.

Oncologists are also beginning to collect young-adult tumor samples that could be examined for chromosomal mutations and other characteristics. Sender, for example, hopes to gather melanoma samples, and Albritton is hunting for colorectal cancers in young adults. She has coaxed her Dana-Farber colleague, cancer geneticist Ronald DePinho, into analyzing the samples. DePinho believes that "there must be something intrinsically wrong with the cancer cells or the host" that makes young adults with colorectal cancer resistant to treatment.

Researchers believe their work could extend beyond AYAs. Just as findings in retinoblastoma, a rare pediatric eye cancer, opened the door to an entire cohort of tumor-suppressor genes, "sometimes the most interesting stuff is at the edges," says Albritton.

A few AYA tumor types have already yielded intriguing patterns. Preliminary data suggest that in Ewing sarcoma, tumors actually form in different parts of the body depending on age: in the extremities among younger patients and in the pelvic region in older ones, where the tumors are more difficult to remove surgically.

At the molecular level, there's growing evidence of a "mixing" of adult and pediatric patterns. In gastrointestinal stromal tumor (GIST), a cancer of the intestinal tract that is most common after age 40, a team at Memorial Sloan-Kettering Cancer Center in New York City 2 years ago described differences in a small sample of children, young adults, and older adults. Young-adult samples, they found, tended to blend qualities of both pediatric GIST, which usually lacks a classic gene mutation, and the adult form.

Rhabdomyosarcoma, which attacks soft tissue and is most common in children, shifts from an embryonic form in younger patients to an alveolar form in older ones. The distinction refers to the cells' genetics and appearance and where they congregate. Like many other pediatric cancers, rhabdomyosarcoma has a worse outcome in older patients, say oncologists.

Thomas is one of the few to focus on the AYA patient's biology. His recently completed study of 14,000 young Australians with various cancers revealed marked gender differences in AYAs. Young women over 15 were 80% more likely to survive than males if they had Ewing sarcoma, 40% more likely to survive if they had osteosarcoma, a bone cancer, and 50% more likely to survive with ALL. In youngsters under 15, gender did not seem linked to survival.

**Seeking answers.** Oncologist Karen Albritton wants to know why 20-somethings with sarcomas fare worse than children.

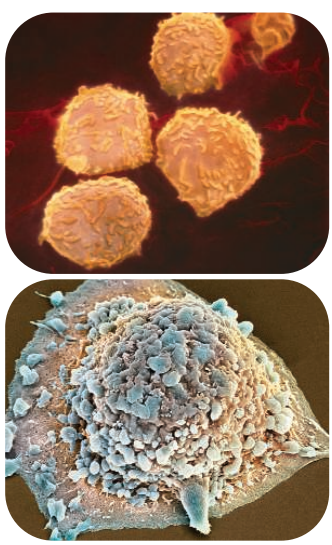
As far as he could tell, possible differences in male behavior—such as being less compliant in therapy—played no role, and Thomas concluded that the key to gender differences is puberty. For example, adolescent and young adult women have a higher percentage of body fat than males, which may affect the distribution of chemotherapy drugs; there may also be differences in drug metabolism. Thomas wonders whether the effective dose reaching tumors is higher for young females than for males. "Until we understand the biological differences" of the patient and the tumor, "we are not treating these cancers optimally," says Bleyer.

That's been evident since 2000, when Wendy Stock, director of the leukemia program at the University of Chicago in Illinois, presented new findings at a cancer meeting. She and a Chicago colleague, pediatric oncologist James Nachman, examined ALL trials conducted over the last 10 years by two cancer cooperative groups, one pediatric and one adult. Children, who can tolerate more intensive treatment, received a different chemotherapy regimen than adults, as is standard. Some AYAs were treated as children, some as adults, depending on which cooperative group they'd fallen into. Stock and Nachman examined the survival of 16- to 21-year-olds and found that those with ALL who enrolled in adult trials had a survival rate of 38%, about the same as older individuals. In the pediatric trials, their survival rate was 68%.

"Honestly, it was such a tremendous shock to us," says Stock. Researchers in France, Germany, and Italy subsequently reviewed their own ALL trials and encountered a nearly identical survival gap.

Oncologists floated several possible explanations, none reassuring. One is that they had been treating AYAs as though their bodies, and even their leukemia, were "adult" when really they were pediatric and ought to have received the regimen given to children. Another possibility is that the pediatricians, who encounter ALL more often than any other cancer, simply do a better job of treating it.

To learn more, Richard Larson, an oncologist who oversees clinical research in hematologic malignancies at the University of Chicago, is running an ALL clinical trial funded by the National Cancer Institute. It aims to enroll 300 16- to 29-year-olds starting this fall. Patients will be treated on a pediatric protocol by adult oncologists and will be compared with 16- to 21-year-olds with ALL in a separate ongoing trial who are receiving the same treatment from pediatricians. The key question, says Larson, is whether the survival rate can be linked to differences in a doctor's age-based specialty. The study is the first anyone can recall that focuses exclusively on young adults.



**Distinctive?** Scientists are wondering whether lymphoblastic leukemia (*top*) and colon cancer manifest differently in older teens and young adults than in other ages.

Meanwhile, the Stock and Nachman review has raised another troubling question: Have oncologists been undertreating adults across the board? With that in mind, Dana-Farber physicians are now experimenting with treating even adults up to age 50 with leukemia on a pediatric regimen.

Still debated is whether altering treatment will by itself erase the ALL survival gap. Sender believes that it's unlikely to be as simple as switching 30-year-olds to a pediatric regimen because "the leukemia has changed" fundamentally in these patients. Hartung's family will be raising funds to help uncover answers she did not live to see. Says her mother, Toni: "Her cause has become ours now." **–JENNIFER COUZIN**

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